

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/18361 A2

BN

(51) International Patent Classification⁷: C07D 311/74,
335/06, 215/06, C07C 229/46, 65/19, C07D 217/04, C07C
57/38, C07D 521/00, C07C 59/82, A61K 31/47, 31/352,
31/192, A61P 29/00, 31/12

(21) International Application Number: PCT/US01/25443

(22) International Filing Date: 14 August 2001 (14.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/651,235	29 August 2000 (29.08.2000)	US
09/651,004	29 August 2000 (29.08.2000)	US
09/651,003	29 August 2000 (29.08.2000)	US
09/651,564	29 August 2000 (29.08.2000)	US
09/651,234	29 August 2000 (29.08.2000)	US
09/651,234	29 August 2000 (29.08.2000)	US
09/651,001	29 August 2000 (29.08.2000)	US
09/651,566	29 August 2000 (29.08.2000)	US

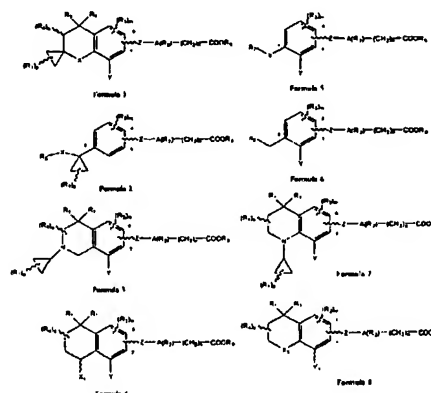
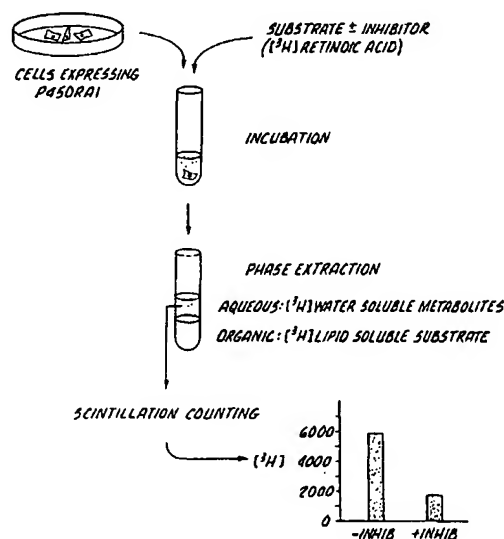
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AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

Published:

— without international search report and to be republished
upon receipt of that report

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(54) Title: COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF CYTOCHROME P450RAI



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(57) Abstract: Compounds having the Formulas 1 through 8, wherein the symbols have the meaning defined in the specification are inhibitors of the cytochrome P450RAI (retinoic acid inducible) enzyme, and are used for treating diseases responsive to treatment by retinoids.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

1 COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF
2 CYTOCHROME P450RAI

3 BACKGROUND OF THE INVENTION

4 1. Field of the Invention

5 The present invention is directed to novel compounds which inhibit
6 the enzyme cytochrome P450RAI. More particularly, the present invention
7 is directed to compounds many of which are derivatives of phenylacetic or
8 heteroarylacetic acid, and which inhibit the enzyme cytochrome P450RAI.
9 Several compounds of the invention that have an inhibitory effect on the
10 enzyme cytochrome P450RAI include a cyclopropyl aryl, cyclopropyl-
11 heteroaryl, cyclopropylaminoaryl, or (1-imidazolyl) methylaryl structure.

12 BACKGROUND ART

13 Compounds which have retinoid-like activity are well known in the
14 art, and are described in numerous United States and other patents and in
15 scientific publications. It is generally known and accepted in the art that
16 retinoid-like activity is useful for treating animals of the mammalian species,
17 including humans, for curing or alleviating the symptoms and conditions of
18 numerous diseases and conditions. In other words, it is generally accepted
19 in the art that pharmaceutical compositions having a retinoid-like compound
20 or compounds as the active ingredient are useful as regulators of cell
21 proliferation and differentiation, and particularly as agents for treating
22 skin-related diseases, including, actinic keratoses, arsenic keratoses,
23 inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other
24 keratinization and hyperproliferative disorders of the skin, eczema, atopic
25 dermatitis, Darriers disease, lichen planus, prevention and reversal of
26 glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin
27 anti-pigmentation agents and to treat and reverse the effects of age and
28 photo damage to the skin. Retinoid compounds are also useful for the
29 prevention and treatment of cancerous and precancerous conditions,

1 including, premalignant and malignant hyperproliferative diseases such as
2 cancers of the breast, skin, prostate, cervix, uterus, colon, bladder,
3 esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic system,
4 metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the
5 mucous membranes and in the treatment of Kaposi's sarcoma. In addition,
6 retinoid compounds can be used as agents to treat diseases of the eye,
7 including, without limitation, proliferative vitreoretinopathy (PVR), retinal
8 detachment, dry eye and other corneopathies, as well as in the treatment and
9 prevention of various cardiovascular diseases, including, without limitation,
10 diseases associated with lipid metabolism such as dyslipidemias, prevention
11 of post-angioplasty restenosis and as an agent to increase the level of
12 circulating tissue plasminogen activator (TPA). Other uses for retinoid
13 compounds include the prevention and treatment of conditions and diseases
14 associated with human papilloma virus (HPV), including warts and genital
15 warts, various inflammatory diseases such as pulmonary fibrosis, ileitis,
16 colitis and Krohn's disease, neurodegenerative diseases such as Alzheimer's
17 disease, Parkinson's disease and stroke, improper pituitary function,
18 including insufficient production of growth hormone, modulation of
19 apoptosis, including both the induction of apoptosis and inhibition of T-Cell
20 activated apoptosis, restoration of hair growth, including combination
21 therapies with the present compounds and other agents such as Minoxidil^R,
22 diseases associated with the immune system, including use of the present
23 compounds as immunosuppressants and immunostimulants, modulation of
24 organ transplant rejection and facilitation of wound healing, including
25 modulation of chelosis. Retinoid compounds have relatively recently been
26 also discovered to be useful for treating type II non-insulin dependent
27 diabetes mellitus (NIDDM).

28 Several compounds having retinoid-like activity are actually

1 marketed under appropriate regulatory approvals in the United States of
2 America and elsewhere as medicaments for the treatment of several diseases
3 responsive to treatment with retinoids. Retinoic acid (RA) itself is a natural
4 product, biosynthesized and present in a multitude of human and
5 mammalian tissues and is known to play an important rule in the regulation
6 of gene expression, tissue differentiation and other important biological
7 processes in mammals including humans. Relatively recently it has been
8 discovered that a catabolic pathway in mammals, including humans, of
9 natural retinoic acid includes a step of hydroxylation of RA catalyzed by the
10 enzyme Cytochrome P450RAI (retinoic acid inducible).

11 Several inhibitors of CP450RAI have been synthesized or discovered
12 in the prior art, among the most important ones ketoconazole, liarozole and
13 R116010 are mentioned. The chemical structures of these prior art
14 compounds are provided below. It has also been noted in the prior art, that
15 administration to mammals, including humans, of certain inhibitors of CP-
16 450RAI results in significant increase in endogeneous RA levels, and
17 further that treatment with CP450RAI inhibitors, for example with liarozole,
18 gives rise to effects similar to treatment by retinoids, for example
19 amelioration of psoriasis.

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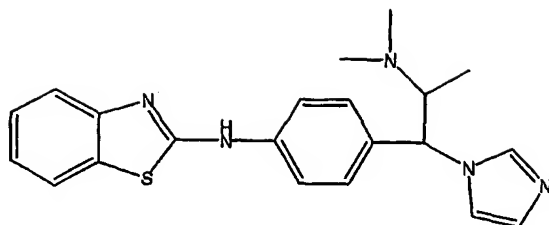
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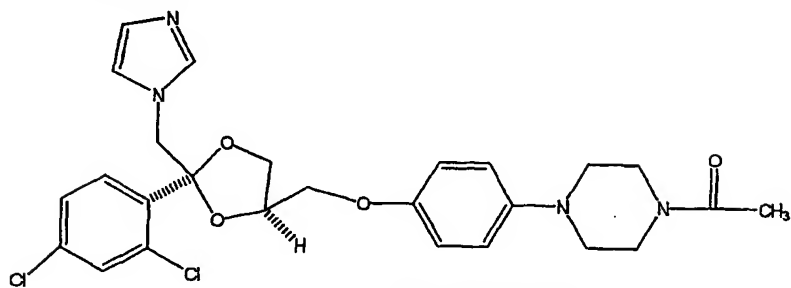
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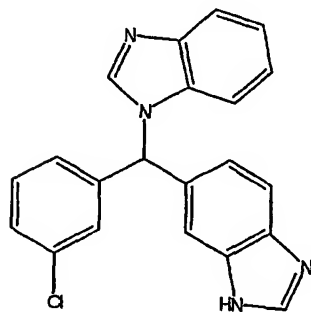
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R116010



KETOCONAZOLE



LIARAZOLE

1 The following publications describe or relate to the above-
2 summarized role of CP450RAI in the natural catabolism of RA, to inhibitors
3 of CP-450RAI and to *in vitro* and *in vivo* experiments which demonstrate
4 that inhibition of CP450RAI activity results in a increases endogeneous RA
5 levels and potential therapeutic benefits:
6 *Kuijpers, et al.*, "The effects of oral liarozole on epidermal proliferation and
7 differentiation in severe plaque psoriasis are comparable with those of
8 acitretin", British Journal of Dermatology, (1998) 139: pp 380-389.
9 *Kang, et al.*, "Liarozole Inhibits Human Epidermal Retinoid Acid 4-
10 Hydroxylase Activity and Differentially Augments Human Skin Responses
11 to Retinoic Acid and Retinol *In Vivo*", The Journal of Investigative
12 Dermatology, (August 1996) Vol. 107, No. 2: pp 183-187.
13 *VanWauwe, et al.*, "Liarozole, an Inhibitor of Retinoic Acid Metabolism,
14 Exerts Retinoid-Mimetic Effects *in Vivo*", The Journal of Pharmacology and
15 Experimental Therapeutics, (1992) Vol. 261, No 2: pp 773-779.
16 *De Porre, et al.*, "Second Generation Retinoic Acid Metabolism Blocking
17 Agent (Ramba) R116010: Dose Finding in Healthy Male Volunteers",
18 University of Leuven, Belgium, pp 30.
19 *Wauwe, et al.*, "Ketoconazole Inhibits the *in Vitro* and *in Vivo* Metabolism of
20 All-*Trans*-Retinoic Acid", The Journal of Pharmacology and Experimental
21 Therapeutics, (1988) Vol. 245, No. 2: pp 718-722.
22 *White, et al.*, "cDNA Cloning of Human Retinoic Acid-metabolizing
23 Enzyme (hP450RAI) Identifies a Novel Family of Cytochromes P450
24 (CYP26)*", The Journal of Biological Chemistry, (1997) Vol. 272, No. 30,
25 Issue of July 25 pp 18538-18541.
26 *Hanzlik, et al.*, "Cyclopropylamines as Suicide Substrates for Cytochromes
27 P450RAI", Journal of Medicinal Chemistry (1979), Vol. 22, No. 7, pp 759-

1 761.

2 *Ortiz de Montellano*, "Topics in Biology - The Inactivation of Cytochrome
3 P450RAI", Annual Reports in Medicinal Chemistry, (1984), Chapter 20, pp
4 201-210.

5 *Hanzlik, et al.* "Suicidal Inactivation of Cytochrome P450RAI by
6 Cyclopropylamines> Evidence for Cation-Radical Intermediates", J. Am.
7 Chem. Soc., (1982), Vol. 104, No. 107, pp. 2048-2052.

8 The present invention provides several new chemical compounds
9 which act as inhibitors of CP450RAI, and as such potentially provide
10 therapeutic benefit in the treatment or prevention of the diseases and
11 conditions which respond to treatment by retinoids and or which in healthy
12 mammals, including humans, are controlled by natural retinoic acid. The
13 perceived mode of action of these compounds is that by inhibiting the
14 enzyme CP450RAI that catabolyzes natural RA, endogenous RA level is
15 elevated to a level where desired therapeutic benefits are attained. The
16 chemical structures of the compounds of the invention are summarized by
17 **Formulas 1 through 8** which are provided in the Summary Section of this
18 application for patent. Based on these chemical structures the following art
19 is of interest as background to the novel structures.

20 U.S. Patent Nos. 5,965,606; 6,025,388; 5,773,594; 5,675,024;
21 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,089,509; 5,616,712;
22 5,134,159; 5,346,895; 5,346,915; 5,149,705; 5,399,561; 4,980,369;
23 5,015,658; 5,130,335; 4,740,519; 4,826,984; 5,037,825; 5,466,861;
24 WO 85/00806; EP 0 130,795; DE 3316932; DE 3708060; *Dawson, et al.*
25 "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,
26 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 1.**

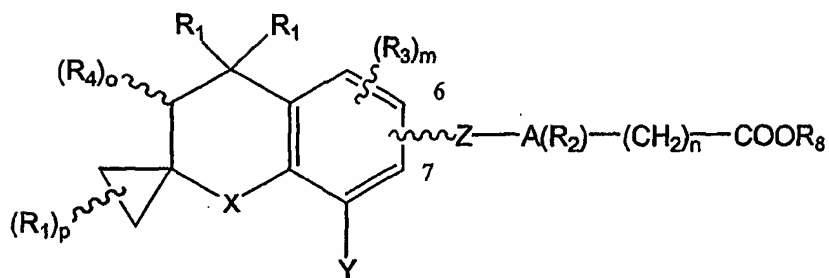
27 U.S. Patent Nos. 5,965,606; 5,534,641; 5,663,357; 5,013,744;
28 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795; 4,992,468;

1 4,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;
2 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;
3 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.*
4 "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,
5 Inc., 1990, pages 324-356; are of interest to compounds of **Formula 2.**
6 *Dawson, et al.* "Chemistry and Biology of Synthetic Retinoids",
7 published by CRC Press, Inc., (1990), pages 324-356; is of interest to
8 compounds of **Formula 3.**
9 U.S. Patent Nos. 5,965,606; 5,773,594; 5,675,024; 5,663,347;
10 5,023,341; 5,264,578; 5,089,509; 5,149,705; 5,130,335; 4,740,519;
11 4,826,969; 4,833,240; 5,037, 825; 5,466,861; 5,559,248; WO 85/00806;
12 WO 92/06948; WO 95/04036; WO 96/05165; EP 0 098 591; EP 0 170 105;
13 EP 0 176 034; EP 0 253,302; EP 0 303 915; EP 0 514 269; EP 0 617 020;
14 EP 0 619 116; EP 0 661 259; DE 3316932; DE 3602473; DE 3715955; UK
15 application GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), 37, 1508-
16 1517; *Graupner et al.* Biochem. and Biophysical Research
17 Communications, (1991), 1554-1561; *Kagechika, et al.*, J. Med. Chem.,
18 (1988), 31, 2182-2192; *Dawson, et al.* "Chemistry and Biology of Synthetic
19 Retinoids", published by CRC Press, Inc., (1990), pages 324-356; are of
20 interest to compounds of **Formula 4.**
21 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;
22 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795;
23 4,992,468; 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;
24 WO 92/06948; EP 0 170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;
25 EP 0 619 116; DE 3524199; Derwent JP6072866; *Dawson, et al.*
26 "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,
27 Inc., (1990), pages 324-356; are of interest to compounds of **Formula 5.**
28 U.S. Patent Nos. 5,965,606; 6,025,388; 5,534,641; 5,663,357;

1 5,013,744; 5,326,898; 5,202,471; 5,391,753; 5,434,173; 5,498,795;
2 4,992,468; 5,723,028; 4,855,320; 5,563,292; WO 85/04652; WO 91/16051;
3 WO 92/06948; EP 0.170 105; EP 0 286 364; EP 0 514 269; EP 0 617 020;
4 EP 0 619 116; DE 3524199; Derwert JP6072866; *Dawson, et al.*
5 "Chemistry and Biology of Synthetic Retinoids", published by CRC Press,
6 Inc., (1990), pages 324-356; is of interest to compounds of **Formula 6.**
7 U.S. Patent Nos. 6,048,873; 5,663,347; 5,045,551; 5,023,341;
8 5,739,338; 5,264,578; 5,089,509; 5,616,712; 5,399,561; 4,826,984;
9 5,037,825; EP 0 130 795; DE 3316932; *Dawson, et al.* "Chemistry and
10 Biology of Synthetic Retinoids", published by CRC Press, Inc., (1990),
11 pages 324-356; are of interest to compounds of **Formula 7.**
12 U.S. Patent Nos. 5,965,606; 5,998,471; 5,773,594; 5,675,024;
13 5,663,347; 5,045,551; 5,023,341; 5,264,578; 5,134,159; 5,346,895;
14 5,346,915; 5,149,705; 5,399,561; 4,980,369; 5,130,335; 4,326,055;
15 4,539,154; 4,740,519; 4,826,969; 4,826,984; 4,833,240; 5,037,825;
16 5,466,861; 5,559,248; WO 85/00806; WO 92/06948; WO 95/04036;
17 WO 96/05165; EP 0 098 591; EP 0 130 795; EP 0 176 034; EP 0 253 302;
18 EP 0 303 915; EP 0 514 269; EP 0 617 020; EP 0 619 116; EP 0 661 259;
19 DE 3316932; DE 3602473; DE 3708060; DE 3715955; U.K. application
20 GB 2190378; *Eyrolles et al.*, J. Med. Chem., (1994), **37** 1508, 1517;
21 *Graupner et al.*, Biochem. and Biophysical Research Communications,
22 (1991) 1554-1561; *Kagechika, et al.*, J. Med. Chem., (1988), **31**, 2182-
23 2192; *Dawson, et al.* "Chemistry and Biology of Synthetic Retinoids",
24 published by CRC Press, Inc., (1990), pages 324-356; are of interest to
25 compounds of **Formula 8.**

SUMMARY OF THE INVENTION

The present invention relates to compounds of **Formula 1**



Formula 1

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is $-C\equiv C-$,

$-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

$-CO-NR_1-$,

NR_1-CO- ;

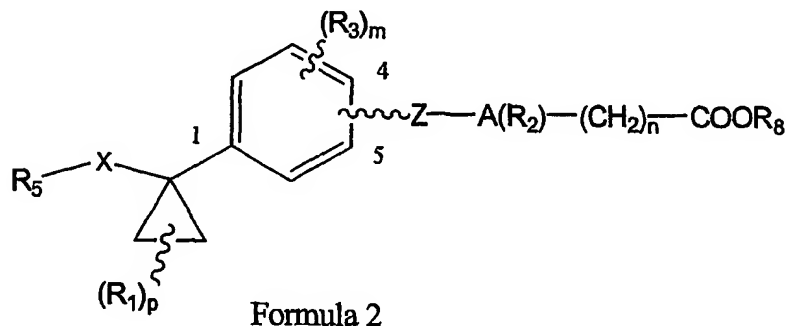
$-CO-O-$,

$-O-CO-$,

$-CS-NR_1-$,

- 1 $\text{NR}_1\text{-CS-}$,
 2 -CO-S- ,
 3 -S-CO- ,
 4 -N=N- ;
 5 R_1 is independently H or alkyl of 1 to 6 carbons;
 6 p is an integer having the values of 0 to 4;
 7 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 ,
 8 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
 9 alkylthio of 1 to 6 carbons;
 10 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 11 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
 12 alkylthio of 1 to 6 carbons or benzyl;
 13 m is an integer having the values 0 to 2;
 14 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
 15 alkyl of 1 to 6 carbons, or halogen;
 16 o is an integer having the values of 0 to 2;
 17 n is an integer having the values of 0 to 4, and
 18 R_8 is H, alkyl of 1 to 6 carbons, $\text{-CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
 19 pharmaceutically acceptable base.

20 The present invention also relates to compounds of **Formula 2**

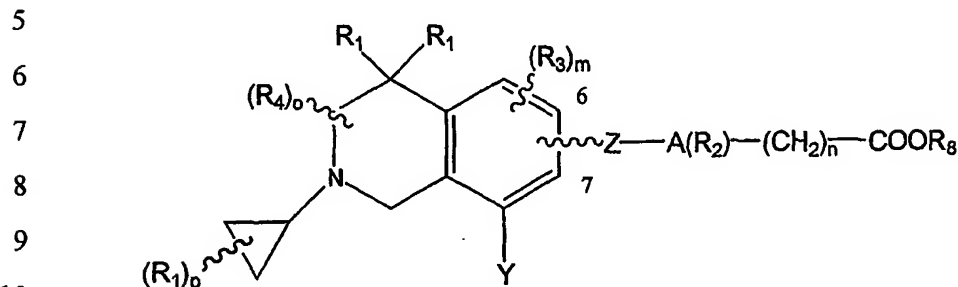


- 1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
2 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
4 heteroaryl groups being optionally substituted with one or two R_2 groups;
5 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;
6 Z is $-C\equiv C-$,
7 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,
8 $-CO-NR_1-$,
9 NR_1-CO- ,
10 $-CO-O-$,
11 $-O-CO-$,
12 $-CS-NR_1-$,
13 NR_1-CS- ,
14 $-CO-S-$,
15 $-S-CO-$,
16 $-N=N-$;
17 R_1 is independently H or alkyl of 1 to 6 carbons;
18 p is an integer having the values of 0 to 4;
19 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
20 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
21 to 6 carbons;
22 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
23 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
24 alkylthio of 1 to 6 carbons or benzyl;
25 m is an integer having the values 0 to 4;
26 R_5 is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6
27 carbons, benzyl, or lower alkyl or halogen substituted benzyl;

1 n is an integer having the values of 0 to 4, and

2 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
3 pharmaceutically acceptable base.

4 The present invention relates to compounds of Formula 3



11 Formula 3

12
13 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
14 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
15 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and
16 heteroaryl groups being optionally substituted with one or two R_2 groups;

17 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
18 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of
19 3 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br,
20 or I;

21 Z is $-\text{C}\equiv\text{C}-$,

22 $-(\text{CR}_1=\text{CR}_1)_n$, where n is an integer having the value 1 - 5,

23 $-\text{CO}-\text{NR}_1-$,

24 $\text{NR}_1-\text{CO}-$,

25 $-\text{CO}-\text{O}-$,

26 $-\text{O}-\text{CO}-$,

27 $-\text{CS}-\text{NR}_1-$,

1 NR₁-CS-,

2 -CO-S-,

3 -S-CO-,

4 -N=N-;

5 R₁ is independently H or alkyl of 1 to 6 carbons;

6 p is an integer having the values of 0 to 5;

7 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
8 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
9 to 6 carbons;

10 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
11 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
12 alkylthio of 1 to 6 carbons or benzyl;

13 m is an integer having the values 0 to 2;

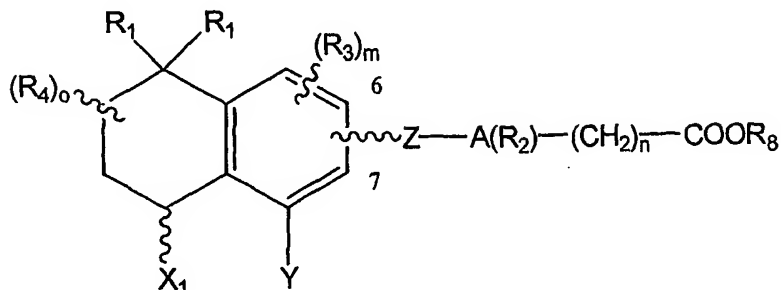
14 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
15 alkyl of 1 to 6 carbons, or halogen;

16 o is an integer having the values of 0 to 4;

17 n is an integer having the values of 0 to 4, and

18 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
19 pharmaceutically acceptable base.

The present invention also relates to compounds of Formula 4



Formula 4

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

X_1 is 1-imidazolyl, or lower alkyl or halogen substituted 1-imidazolyl, OR, SR, NRR_6 where R is H, alkyl of 1 to 6 carbons or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is $-C\equiv C-$,

$-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,

$-CO-NR_1-$,

NR_1-CO- ,

$-CO-O-$,

$-O-CO-$,

$-CS-NR_1-$,

1 NR₁-CS-,

2 -CO-S-,

3 -S-CO-,

4 -N=N-;

5 R₁ is independently H or alkyl of 1 to 6 carbons;

6 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
7 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
8 to 6 carbons;

9 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
11 alkylthio of 1 to 6 carbons or benzyl;

12 m is an integer having the values 0 to 2;

13 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
14 alkyl of 1 to 6 carbons, or halogen;

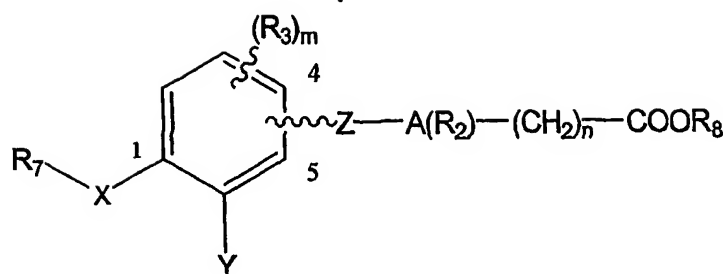
15 o is an integer having the values of 0 to 4;

16 R₆ is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl
17 substituted cycloalkyl of 3 to 6 carbons;

18 n is an integer having the values of 0 to 4, and

19 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
20 pharmaceutically acceptable base, with the proviso that when Y is H, A is
21 phenyl and X₁ is OH then n is 1 to 4.

22 The present invention also relates to compounds of Formula 5



Formula 5

wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

X is O, S or NR where R is H, alkyl of 1 to 6 carbons, C_{1-6} -trialkylsilyl or benzyl;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br, or I;

Z is $-C\equiv C-$,
 $-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,
 $-CO-NR_1-$,
 NR_1-CO- ,
 $-CO-O-$,
 $-O-CO-$,
 $-CS-NR_1-$,
 NR_1-CS- ,
 $-CO-S-$,
 $-S-CO-$,
 $-N=N-$;

17.

1 R_1 is independently H or alkyl of 1 to 6 carbons;

2 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
3 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
4 to 6 carbons;

5 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
6 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
7 alkylthio of 1 to 6 carbons or benzyl;

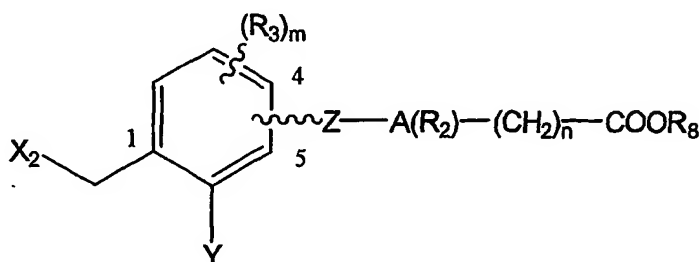
8 m is an integer having the values 0 to 3;

9 R_7 is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower
10 alkyl substituted cycloalkyl of 1 to 6 carbons;

11 n is an integer having the values of 1 to 4, and

12 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
13 pharmaceutically acceptable base.

14 The present invention also relates to compounds of Formula 6



Formula 6

22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and
25 heteroaryl groups being optionally substituted with one or two R_2 groups;

26 X_2 is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,
27 OR_7 , SR_7 or NRR_7 where R is H, alkyl of 1 to 6 carbons or benzyl;

1 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 2 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of
 3 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,
 4 or I;

5 Z is -C≡C-,
 6 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,
 7 -CO-NR₁-,
 8 NR₁-CO-,
 9 -CO-O-,
 10 -O-CO-,
 11 -CS-NR₁-,
 12 NR₁-CS-,
 13 -CO-S-,
 14 -S-CO-,
 15 -N=N-;

16 R₁ is independently H or alkyl of 1 to 6 carbons;

17 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 18 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
 19 to 6 carbons;

20 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
 21 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
 22 alkylthio of 1 to 6 carbons or benzyl;

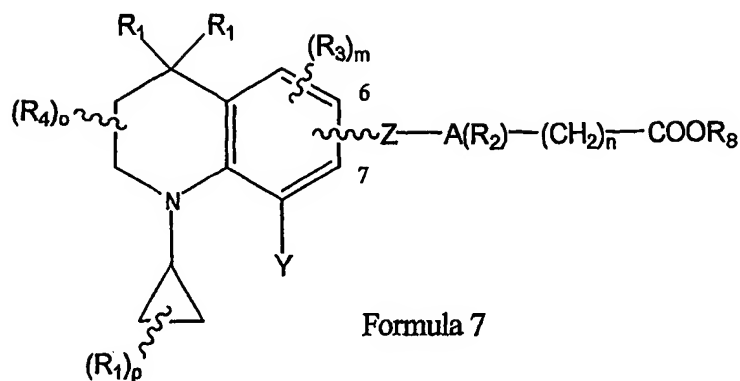
23 m is an integer having the values 0 to 3;

24 R₇ is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower
 25 alkyl substituted cycloalkyl of 3 to 6 carbons or C₁₋₆-trialkylsilyl.

26 n is an integer having the values of 0 to 4, and

27 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
 28 pharmaceutically acceptable base.

The present invention also relates to compounds of **Formula 7**



wherein A is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl, Br, or I;

Z is $-C\equiv C-$,

$-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,

$-CO-NR_1-$,

NR_1-CO- ,

$-CO-O-$,

$-O-CO-$,

$-CS-NR_1-$,

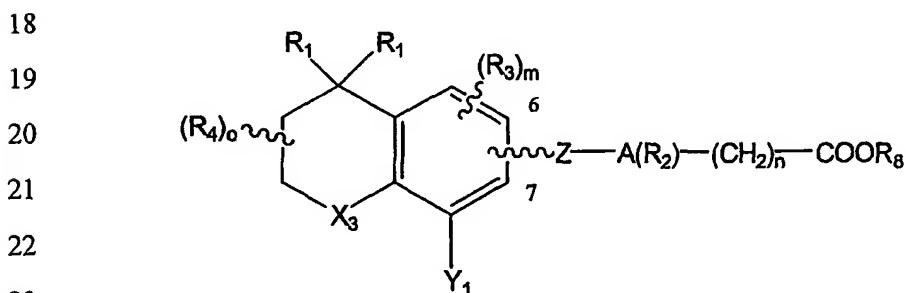
NR_1-CS- ,

$-CO-S-$,

$-S-CO-$,

- 1 -N=N-;
- 2 R_1 is independently H or alkyl of 1 to 6 carbons;
- 3 p is an integer having the values of 0 to 5;
- 4 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 ,
 5 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
 6 alkylthio of 1 to 6 carbons;
- 7 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro
 8 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
 9 alkylthio of 1 to 6 carbons or benzyl;
- 10 m is an integer having the values 0 to 2;
- 11 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
 12 alkyl of 1 to 6 carbons, or halogen;
- 13 o is an integer having the values of 0 to 4;
- 14 n is an integer having the values of 0 to 4, and
- 15 R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a
 16 pharmaceutically acceptable base.

17 The present invention also relates to compounds of **Formula 8**



24 **Formula 8**

25 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
 26 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
 27 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and

1 heteroaryl groups being optionally substituted with one or two R_2 groups;

2 X_3 is S, or O, $C(R_1)_2$, or CO;

3 Y_1 is H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons,
4 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

5 Z is $-C\equiv C-$,

6 $-(CR_1=CR_1)_n$, where n is an integer having the value 1 - 5,

7 $-CO-NR_1-$,

8 NR_1-CO- ,

9 $-CO-O-$,

10 $-O-CO-$,

11 $-CS-NR_1-$,

12 NR_1-CS- ,

13 $-CO-S-$,

14 $-S-CO-$,

15 $-N=N-$;

16 R_1 is independently H or alkyl of 1 to 6 carbons;

17 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 ,

18 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or

19 alkylthio of 1 to 6 carbons;

20 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro

21 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,

22 alkylthio of 1 to 6 carbons or benzyl;

23 m is an integer having the values 0 to 2;

24 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted

25 alkyl of 1 to 6 carbons, or halogen;

26 o is an integer having the values of 0 to 4;

27 n is an integer having the values of 0 to 4, and

28 R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a

1 pharmaceutically acceptable base, the compound meeting at least one of the
2 provisos selected from the group consisting of:

3 Y_1 is cycloalkyl,
4 when Y_1 is not cycloalkyl then X_3 is O or S and n is 1,
5 when Y_1 is not cycloalkyl then X_3 is CO, and n is 1,
6 when Y_1 is not cycloalkyl then X_3 is CO and the moiety A is
7 substituted with at least one F group.

8 In a second aspect, this invention relates to the use of the compounds
9 of **Formula 1** through **Formula 8** for the prevention or treatment of
10 diseases and conditions in mammals, including humans, which diseases or
11 conditions are prevented, treated, ameliorated, or the onset of which is
12 delayed by administration of retinoid compounds or by the mammalian
13 organism's naturally occurring retinoic acid. Because the compounds act as
14 inhibitors of the breakdown of retinoic acid, the invention also relates to the
15 use of the compounds of **Formula 1** through **Formula 8** in conjunction
16 with retinoic acid or other retinoids. In this regard it is noted that retinoids
17 are useful for the treatment of skin-related diseases, including, without
18 limitation, actinic keratoses, arsenic keratoses, inflammatory and
19 non-inflammatory acne, psoriasis, ichthyoses and other keratinization and
20 hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers
21 disease, lichen planus, prevention and reversal of glucocorticoid damage
22 (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation
23 agents and to treat and reverse the effects of age and photo damage to the
24 skin. The retinoids are also useful for the prevention and treatment of
25 metabolic diseases such as type II non-insulin dependent diabetes mellitus
26 (NIDDM) and for prevention and treatment of cancerous and precancerous
27 conditions, including, premalignant and malignant hyperproliferative
28 diseases such as cancers of the breast, skin, prostate, cervix, uterus, colon,

1 bladder, esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic
2 system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of
3 the mucous membranes and in the treatment of Kaposi's sarcoma. Retinoids
4 can also be used as agents to treat diseases of the eye, including, without
5 limitation, proliferative vitreoretinopathy (PVR), retinal detachment, dry eye
6 and other corneopathies, as well as in the treatment and prevention of
7 various cardiovascular diseases, including, without limitation, diseases
8 associated with lipid metabolism such as dyslipidemias, prevention of
9 post-angioplasty restenosis and as an agent to increase the level of
10 circulating tissue plasminogen activator (TPA). Other uses for retinoids
11 include the prevention and treatment of conditions and diseases associated
12 with human papilloma virus (HPV), including warts and genital warts,
13 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and
14 Krohn's disease, neurodegenerative diseases such as Alzheimer's disease,
15 Parkinson's disease and stroke, improper pituitary function, including
16 insufficient production of growth hormone, modulation of apoptosis,
17 including both the induction of apoptosis and inhibition of T-Cell activated
18 apoptosis, restoration of hair growth, including combination therapies with
19 the present compounds and other agents such as Minoxidil^R, diseases
20 associated with the immune system, including use of the present compounds
21 as immunosuppressants and immunostimulants, modulation of organ
22 transplant rejection and facilitation of wound healing, including modulation
23 of chelosis.

24 This invention also relates to a pharmaceutical formulation
25 comprising one or more compounds of **Formula 1** through **Formula 8** in
26 admixture with a pharmaceutically acceptable excipient, said formulation
27 being adapted for administration to a mammal, including a human being, to
28 treat or alleviate the conditions which were described above as treatable by

1 retinoids, or which are controlled by or responsive to the organism's native
2 retinoic acid. These formulations can also be co-administered with retinoids
3 to enhance or prolong the effects of medications containing retinoids or of
4 the organism's native retinoic acid.

5 BRIEF DESCRIPTION OF THE DRAWING FIGURE

6 Figure 1 is a schematic representation of the P450RAI cell based
7 assay utilized to evaluate the ability of the compounds of the invention to
8 inhibit the Cytochrome P450RAI enzyme.

9 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

10 P450RAI-1 Cell-Based Inhibitor Assay:

11 Figure 1 shows a schematic diagram of the P450RAI-1 cell based
12 assay. P450RAI-1 stably transfected HeLa cells are maintained in 100
13 millimolar tissue culture dishes in Modified Eagle's Medium (MEM)
14 containing 10 % Fetal Bovine Serum (FBS) and 100 µg/ml hygromycin.
15 Exponentially growing cells are harvested by incubating in trypsin. Cells are
16 then washed with 1X Phosphate Buffered Saline (PBS) and plated in a 48-
17 well plate at 5 X10⁵ cells in 0.2 ml MEM medium containing 10 % FBS and
18 0.05 µCi [³H]-RA in the presence or absence of increasing concentrations of
19 the test compounds. The compounds are diluted in 100% DMSO and then
20 added in triplicate wells at either 10, 1 or 0.1 µM final concentration. As a
21 positive control for RA metabolism inhibition, cells are also incubated with
22 ketoconazole at 100, 10 and 1 µM. Cells are incubated for 3 hours at 37°C.
23 The retinoids are then extracted using the procedure of *Bligh et al.* (1959)
24 Canadian Journal of Biochemistry 37, 911-917, modified by using
25 methylenechloride instead of chloroform. The publication *Bligh et al.*
26 (1959) Canadian Journal of Biochemistry 37, 911-917 is specifically
27 incorporated herein by reference. The water soluble radioactivity is

1 quantified using a β -scintillation counter. IC_{50} values represent the
2 concentration of inhibitor required to inhibit all-*trans*-RA metabolism by 50
3 percent and are derived manually from log-transformed data. The IC_{50}
4 values obtained in this assay for several preferred compounds of the
5 invention are disclosed in Table 1 below.

6 Assays of Retinoid-like or Retinoid Antagonist and Inverse Agonist-
7 like Biological Activity

8 Assays described below measure the ability of a compound to bind
9 to, and/or activate various retinoid receptor subtypes. When in these assays
10 a compound binds to a given receptor subtype and activates the transcription
11 of a reporter gene through that subtype, then the compound is considered an
12 **agonist** of that receptor subtype. Conversely, a compound is considered an
13 **antagonist** of a given receptor subtype if in the below described
14 co-transfection assays the compound does not cause significant
15 transcriptional activation of the receptor regulated reporter gene, but
16 nevertheless binds to the receptor with a K_d value of less than approximately
17 1 micromolar. In the below described assays the ability of the compounds to
18 bind to RAR_{α} , RAR_{β} , RAR_{γ} , RXR_{α} , RXR_{β} and RXR_{γ} receptors, and the
19 ability or inability of the compounds to activate transcription of a reporter
20 gene through these receptor subtypes can be tested.

21 As far as specific assays are concerned, a **chimeric receptor**
22 **transactivation** assay which tests for agonist-like activity in the RAR_{α} ,
23 RAR_{β} , and RAR_{γ} receptor subtypes, and which is based on work published
24 by Feigner P. L. and Holm M. (1989) Focus, 112 is described in detail in
25 United States Patent No. 5,455,265. The specification of United States
26 Patent No. 5,455,265 is hereby expressly incorporated by reference. The
27 numeric results obtained with several preferred compounds of this

1 invention in this assay are shown below in **Table 1**. These data demonstrate
2 that generally speaking the compounds are not agonists (or only weak
3 agonists) of RAR retinoic receptors, and also that they do not bind, or in
4 some cases bind only weakly to RAR retinoid receptors.

5 A **holoreceptor transactivation assay** and a **ligand binding assay**
6 which measure the antagonist/agonist like activity of the compounds of the
7 invention, or their ability to bind to the several retinoid receptor subtypes,
8 respectively, are described in published PCT Application No. WO
9 WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published on June
10 24, 1993, the specification of which is also incorporated herein by reference.
11 A detailed experimental procedure for holoreceptor transactivations has
12 been described by *Heyman et al. Cell* 68, 397 - 406, (1992); *Allegretto et*
13 *al. J. Biol. Chem.* 268, 26625 - 26633, and *Mangelsdorf et al. The*
14 *Retinoids: Biology, Chemistry and Medicine*, pp 319 - 349, Raven Press
15 Ltd., New York, which are expressly incorporated herein by reference. The
16 results obtained in this assay are expressed in EC₅₀ numbers, as they are
17 also in the **chimeric receptor transactivation assay**. The results of **ligand**
18 **binding assay** are expressed in K_d numbers. (See *Cheng et al. Biochemical*
19 *Pharmacology* Vol. 22 pp 3099-3108, expressly incorporated herein by
20 reference.)

21 The results if the ligand binding assay for several preferred
22 compounds of the invention are included in **Table 1**. In the **holoreceptor**
23 **transactivation assay**, tested for RXR_α, RXR_β, and RXR_γ receptors, the
24 compounds of the present invention are, generally speaking, entirely devoid
25 of activity, demonstrating that the compounds of the invention do not act as
26 RXR agonists.

TABLE 1

Compound #	General Formula	Table # ¹	RAR EC ₅₀ /(EFFICACY)/K _d nM			P450RAI INHIBITION DATA
			α	β	γ	INTACT HELA IC ₅₀ μ M
110	2	3	NA 2058	74 (44) 409	262 (42) >10K	>10
112	2	3	NA 5853	335 (37) 704	NA 685	>10
3	4	5	280 (28) 145	4.8 (54) 0.8	9.8 (52) 158	3
114	2	3	NA >10K	NA >10K	NA >10K	>10
108	2	3	6.6 (15) 21K	283 (36) 547	141 (10) 13K	>10
116	2	3	NA 3269	WA 732	NA 886	>10
77	2	3	NA 2207	WA 225	NA 16	>10
78	2	3	NA >10K	NA >10K	NA >10K	>10
40	1	2	33 (207) 69	1.2 (126) 1.3	6.8 (140) 363	1.7
42	1	2	NA 15K	NA 3636	NA >10K	0.19

1	28	8	9	NA 21K	NA 4272	NA >10K	0.34
2	70	2	3	NA >10K	NA >10K	NA >10K	>10
3	69	2	3	313 (10) 469	12 (50) 133	52.6 (31) 501	>10
4	73	2	3	WA 486	22.5 (39) 26	91 (24) 351	>10
5	74	2	3	NA 11K	NA 14K	NA >10K	3.5
6	30	8	9	14	2.2	84	0.28
7	44	1	2	49 (138) 37	1.7 (100) 1.9	7.5 (116) 392	0.27
8	82	2	3	NA >10K	NA >10K	NA >10K	>10
9	81	2	3	NA 4210	490 (80) 846	183 (67) 1058	>10
10	89	2	3	268 (20) 3407	26 (50) 980	12 (46) 475	>10
11	90	2	3	NA >10K	NA >10K	NA >10K	0.95
12	94	2	3	NA >10K	NA >10K	NA >10K	>10

1	93	2	3	4821 (114) 3450	20 (39) 554	10 (55) 358	>10
2	5	8	9	NA 9148	11 (36) 2815	NA >10K	0.55
3	8	4	5	NA 10K	363 (96) 3781	NA 25K	0.4
4	86	2	3	NA >10K	NA >10K	NA >10K	1.4
5	85	2	3	976 (60) 1861	3.5 (77) 240	2.5 (65) 302	>10
6	98	2	3	NA	NA	NA	0.8
7	13	4	5	NA	3.2 (6.6)	116 (9)	3.1
8	10	8	9	57 (146)	0.3 (86)	6 (94)	0.7
9	36	8	9	13K	4896	492	0.033
10	38	8	9	10K	5317	2884	0.025
11	34	8	9	61.5	15	2.5	0.13
12	119	6	7	>10K	>10K	>10K	0.4

30

1	121	6	7				0.18
				>10K	>100K	>100K	
2	46	8	9				2.2
				>10K	>10K	>10K	
3	20	8	9				>10
4	18	4	5				1.1
5	32	8	9				0.18
				27K	4225	13K	
6	139	4	5				0.05
7	22	3	4				1.6
8	24	3	4				3
9	137	4	5				0.1
10	26	4	5				10
11	127	6	7				0.4
12	126	6	7				0.09
13	48	1	2				0.03
14	50	1	2				0.014
15	52	1	2				0.05
16	54	1	2				0.022

1	62	7	8				>10
2	56	8	9				0.13
3	134	6	7				5
4	58	1	2				0.18
5	60	1	2				1.6
6	143						0.8
7	145						0.2

8
9 ¹The "Table #" refers to the Table provided below where the compound is
10 identified with reference to a corresponding specific formula of **Formulas 9**
11 through **16**.

TOPICAL SKIN IRRITATION TESTS

As is known the topical retinoid all-trans-retinoic acid (ATRA) and oral retinoids such as 13-cis RA and etretinate are known to induce substantial skin irritation in humans. This irritation is a direct result of activation of the RAR nuclear receptors. Analysis of retinoid topical irritation is also a highly reproducible method of determining *in vivo* retinoid potency. The SKH1-*hrBR* or hairless mouse provides a convenient animal model of topical irritation, since retinoid-induced skin flaking and abrasion can be readily scored by eye (*Standeven et al.*, "Specific antagonist of retinoid toxicity in mice." Toxicol. Appl. Pharmacol., 138:169-175, (1996); *Thacher, et al.*, "Receptor specificity of retinoid-induced hyperplasia. Effect of RXR-selective agonists and correlation with topical irritation". J. Pharm. Exp. Ther., 282:528-534, (1997)). As is demonstrated below the topical application of P450RAI inhibitors of the present invention also causes an increase in the endogenous levels of ATRA that results in ATRA-induced irritation in skin of hairless mice. The attached data table discloses the retinoid-mimetic effects of some P450RAI inhibitor compounds of the present invention on the skin of hairless mice.

Methods

Female hairless mice (Crl:SKH1-*hrBR*), 5-7 weeks old, were obtained from Charles River Breeding Labs (Wilmington, MA). Animals were about 6 weeks old at the start of the experiments. Food (Purina Rodent Chow 5001) and reverse osmosis water were provided *ad libitum*. Mice were housed individually throughout the dosing period. In some experiments, mice that fit within a defined weight range, *e.g.*, 21-25g, were selected from the available stock and then randomly assigned to the various treatment groups, using body weight as the randomization variable.

The compounds to be tested were dissolved in acetone for application

1 to the backs of the mice.

2 Mice were treated topically on the back in a volume of 4.0 ml/kg
3 (0.07-0.12ml) adjusted daily so as to deliver a fixed dose of test compound
4 per g body weight. Doses are disclosed as nmol/25g.

5 Unless indicated otherwise, mice were treated with retinoids once
6 daily on days 1 through 5 and observed on days 2, 3, 4, 5, 6, 7 and 8.

7 The mice were weighed daily and the dorsal skin was graded daily
8 using separate semi-quantitative scales to determine flaking and abrasion.
9 These flaking and abrasion scores were combined with weight change (if
10 any) to create a cutaneous toxicity score (Blackjack score).

11 Cutaneous Toxicity Score

12 A visual grading scale was used for characterizing topical irritation
13 on a daily basis. The grading scale used is as follows:

14 <u>Flaking</u>	<u>Abrasions</u>
15 0 = none	0 = none
16 1 = slight (small flakes, <50% 17 coverage)	1 = slight (one or two abrasions with a light pink color)
18 2 = mild (small flakes, 50% 19 coverage)	2 = mild (several abrasions with a pink color)
20 3 = moderate (small flakes, >50% 21 coverage & large flakes, <25% 22 coverage)	3 = moderate (one or two deep abrasions with red color, <25% coverage)
23 4 = severe (small flakes, >50% 24 coverage & large flakes, 25-50% 25 coverage)	4 = severe (multiple deep abrasions with red color, >25% coverage)
26 5 = very severe (large flakes, >50% 27 coverage)	

28

1 Topical Toxicity Score

2 The flaking and abrasion observations were combined with body
3 weight observations to calculate a single, semiquantitative topical or
4 cutaneous "toxicity score" as detailed below. The toxicity score (also
5 known as "blackjack score" since the theoretical maximum is 21) takes into
6 account the maximal severity, and the time of onset of skin flaking and
7 abrasions and the extent of weight between the first and last days of the
8 experiment. Below are listed the seven numerical components of the
9 toxicity score and an explanation of how those values are combined to
10 calculate the toxicity score.

11 1. Flaking-Maximal Severity:

12 Highest flaking score attained during observation period.

13 2. Flaking-Day of Onset of grade 2 or worse:

14 0 - > 8 days

15 1 - day 8

16 2 - day 6 or 7

17 3 - day 4 or 5

18 4 - day 2 or 3

19 3. Flaking-Average Severity:

20 Flaking severity scores are summed and divided by the number
21 of observation days.

22 4. Abrasion-Maximal Severity:

23 Highest abrasion score attained during observation period.

24 5. Abrasion-Day of Onset of grade 2 or worse:

25 Same scale as (2) above.

26 6. Abrasion-Average Severity:

27 Abrasion severity scores are summed and divided by the
28 number of observation days.

1 7. Systemic Toxicity (weight loss):

2 0 - <1g

3 1 - 1 to 2g

4 2 - 2 to 4g

5 3 - 4 to 6g

6 4 - >6g or dead

7 Calculation of Composite Flaking Score

8 Flaking onset score (2) and average severity score (3) are summed
9 and divided by two. The quotient is added to the maximal severity score (1).
10 Composite flaking scores are calculated for each individual animal in a
11 group, averaged, and rounded to the nearest integer. Values can range from
12 0-9.

13 Calculation of Composite Abrasion Score

14 Abrasion onset score (5) and average severity score (6) are summed
15 and divided by two. The quotient is added to the maximal severity score (4).
16 Composite abrasion scores are calculated for each individual animal in a
17 group, averaged and rounded to the nearest integer. Values can range from
18 0-8.

19 Calculation of Toxicity Score

20 Composite flaking score, composite abrasion score, and systemic
21 toxicity score are summed to give the "toxicity score." Toxicity scores are
22 calculated for each individual animal in a group, averaged, and rounded to
23 the nearest integer. Values can range from 0-21 and are expressed in Table
24 1A below as the mean \pm SD of the values for a group.

25 Calculation of Percentage Change in Body Weight

26 The body weight at the time of the last weighing (day 8, 11, or 12)
27 was subtracted from the initial body weight. The difference was divided by
28 the initial body weight, multiplied by 100%, and rounded to the nearest

integer. Values were calculated for each individual animal and the mean and standard deviation for each group are shown.

TABLE 1A

Compound No.	Cutaneous Toxicity Score (Blackjack Score)		
	100 nmole	300 nmole	1000 nmole
5	0		6±3
15	1 ± 1		5 ± 2
36	1 ± 1		11 ± 0
38	1 ± 1		10 ± 1
8	5 ± 2	8 ± 3	12 ± 1
22	0 ± 0	0 ± 0	1 ± 1
137	1 ± 1	1 ± 1	5 ± 2
48	1 ± 1	3 ± 1	7 ± 2
50	1 ± 0	3 ± 2	8 ± 2
58	0 ± 0	0 ± 0	0 ± 0
131	1 ± 1	0 ± 1	1 ± 1
127	0 ± 0	0 ± 0	0 ± 0
18	0 ± 0	5 ± 2	10 ± 2

Modes of Administration

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations. Thus, in the treatment of dermatoses, it will

1 generally be preferred to administer the drug topically, though in certain
2 cases such as treatment of severe cystic acne or psoriasis, oral administration
3 may also be used. Any common topical formulation such as a solution,
4 suspension, gel, ointment, or salve and the like may be used. Preparation of
5 such topical formulations are well described in the art of pharmaceutical
6 formulations as exemplified, for example, by Remington's Pharmaceutical
7 Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For
8 topical application, these compounds could also be administered as a
9 powder or spray, particularly in aerosol form. If the drug is to be
10 administered systemically, it may be confectioned as a powder, pill, tablet or the
11 like or as a syrup or elixir suitable for oral administration. For intravenous
12 or intraperitoneal administration, the compound will be prepared as a
13 solution or suspension capable of being administered by injection. In
14 certain cases, it may be useful to formulate these compounds by injection.
15 In certain cases, it may be useful to formulate these compounds in
16 suppository form or as extended release formulation for deposit under the
17 skin or intramuscular injection.

18 Other medicaments can be added to such topical formulation for such
19 secondary purposes as treating skin dryness; providing protection against
20 light; other medications for treating dermatoses; medicaments for preventing
21 infection, reducing irritation, inflammation and the like.

22 Treatment of dermatoses or any other indications known or
23 discovered to be susceptible to treatment by retinoic acid-like compounds,
24 or to control by naturally occurring retinoic acid will be effected by
25 administration of the therapeutically effective dose of one or more
26 compounds of the instant invention. A therapeutic concentration will be
27 that concentration which effects reduction of the particular condition, or
28 retards its expansion. In certain instances, the compound potentially may be

1 used in prophylactic manner to prevent onset of a particular condition.
2 A useful therapeutic or prophylactic concentration will vary from
3 condition to condition and in certain instances may vary with the severity of
4 the condition being treated and the patient's susceptibility to treatment.
5 Accordingly, no single concentration will be uniformly useful, but will
6 require modification depending on the particularities of the disease being
7 treated. Such concentrations can be arrived at through routine
8 experimentation. However, it is anticipated that in the treatment of, for
9 example, acne, or similar dermatoses, that a formulation containing between
10 0.01 and 1.0 milligrams per milliliter of formulation will constitute a
11 therapeutically effective concentration for total application. If administered
12 systemically, an amount between 0.01 and 5 mg per kg of body weight per
13 day would be expected to effect a therapeutic result in the treatment of many
14 diseases for which these compounds are useful.

15 In some applications pharmaceutical formulations containing the CP-
16 450RAI inhibitory compounds of the invention may be co-administered
17 with formulations containing retinoids.

18 GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

19 Definitions

20 The term alkyl refers to and covers any and all groups which are
21 known as normal alkyl and branched-chain alkyl. Unless specified
22 otherwise, lower alkyl means the above-defined broad definition of alkyl
23 groups having 1 to 6 carbons in case of normal lower alkyl, and 3 to 6
24 carbons for lower branch chained alkyl groups. A pharmaceutically
25 acceptable salt may be prepared for any compound in this invention having a
26 functionality capable of forming a salt, for example an acid functionality. A
27 pharmaceutically acceptable salt is any salt which retains the activity of the
28 parent compound and does not impart any deleterious or untoward effect on

1 the subject to which it is administered and in the context in which it is
2 administered.

3 Pharmaceutically acceptable salts may be derived from organic or
4 inorganic bases. The salt may be a mono or polyvalent ion. Of particular
5 interest are the inorganic ions, sodium, potassium, calcium, and magnesium.
6 Organic salts may be made with amines, particularly ammonium salts such
7 as mono-, di- and trialkyl amines or ethanol amines. Salts may also be
8 formed with caffeine, tromethamine and similar molecules. Where there is a
9 nitrogen sufficiently basic as to be capable of forming acid addition salts,
10 such may be formed with any inorganic or organic acids or alkylating agent
11 such as methyl iodide. Preferred salts are those formed with inorganic acids
12 such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a
13 number of simple organic acids such as mono-, di- or tri- acid may also be
14 used.

15 Some compounds of the present invention may have *trans* and *cis* (E
16 and Z) isomers. Unless specific orientation of substituents relative to a
17 double bond or a ring is indicated in the name of the respective compound,
18 and/or by specifically showing in the structural formula the orientation of
19 the substituents relative to the double bond or ring the invention covers
20 *trans* as well as *cis* isomers.

21 Some of the compounds of the present invention may contain one or
22 more chiral centers and therefore may exist in enantiomeric and
23 diastereomeric forms. The scope of the present invention is intended to
24 cover all isomers *per se*, as well as mixtures of *cis* and *trans* isomers,
25 mixtures of diastereomers and racemic mixtures of enantiomers (optical
26 isomers) as well. A bond drawn with a wavy line indicates that the carbon
27 to which the bond is attached can be in any of the applicable possible
28 configurations.

1 General Synthetic Methodology

2 The compounds of the invention are encompassed by the general
3 **Formulas 1 through 8** provided above. As it can be seen, in each of these
4 formulas a linker or tethering group designated **Z** covalently connects an
5 aromatic or heteroaromatic moiety designated $A(R_2)-CH_2)_n-COOR_8$ and
6 another cyclic moiety which in accordance with these formulas is a
7 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,
8 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety.
9 Generally speaking a compound such as $X_4-A(R_2)-CH_2)_n-COOR_8$ is
10 commercially available, or can be made in accordance with the chemical
11 literature, or with such modification of known chemical processes which are
12 within the skill of the practicing organic chemist. The group X_4 represents a
13 reactive group, which is suitable for coupling the $X_4-A(R_2)-CH_2)_n-COOR_8$
14 compound to a derivative of the substituted phenyl, substituted
15 tetrahydronaphthalene, substituted chroman, thiochroman,
16 tetrahydroquinoline or tetrahydroisoquinoline moiety so that as a result of
17 the coupling the linker or tether moiety **Z** is formed. In many instances the
18 group X_4 is a leaving group such as halogen, or
19 trifluoromethanesulfonyloxy, or a group capable of participating in a *Wittig*
20 or *Horner Emmons* reaction. In some instances the group X_4 is an ethynyl
21 group capable of undergoing a coupling reaction with a leaving group (such
22 as a halogen or a trifluoromethanesulfonyloxy group) attached to the
23 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,
24 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety. The
25 group X_4 can also represent an OH or an NH_2 group that forms an ester
26 (COO) or amide (CONH) linker, respectively, when reacted with an
27 activated carboxyl derivative of the substituted phenyl, substituted
28 tetrahydronaphthalene, substituted chroman, thiochroman,

1 tetrahydroquinoline or tetrahydroisoquinoline moiety. Examples for the
2 compounds of formula $X_4-A(R_2)-CH_2)_n-COOR_8$ are provided in the
3 specific examples below. Further examples where the X_4 group is halogen
4 are ethyl 4-iodobenzoate, ethyl 6-iodonicotinate, ethyl 5-iodofuran-3-
5 carboxylate, ethyl 5-iodothiophen-3-carboxylate, ethyl 5-iodofuran-2-
6 carboxylate, ethyl 5-iodothiophen-2-carboxylate, and analogous halogenated
7 derivatives of the respective pyridazine, pyrazine and other heteroaryl
8 carboxylic acid esters. The analogous aryl and heteroaryl hydroxyl
9 compounds and amines, wherein the halogen of the above-listed compounds
10 is replaced by OH or NH_2 respectively, also serve as additional examples for
11 the reagents of the formula $X_4-A(R_2)-CH_2)_n-COOR_8$. In these examples
12 X_4 is OH or NH_2 , respectively.

13 Still further in accordance with the general synthetic methodology to
14 provide the compounds of the present invention, a derivative of the
15 substituted phenyl, substituted tetrahydronaphthalene, substituted chroman,
16 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety is
17 synthesized first, having a covalently attached X_5 group. The X_5 group
18 reacts with the X_4 group of the reagent $X_4-A(R_2)-CH_2)_n-COOR_8$ to form
19 the linker designated Z in Formulas 1 through 8. The X_5 group is one that
20 is capable of participating in a catalyzed coupling reaction, (such as an
21 ethynyl group when X_4 is a leaving group), or a leaving group (such as
22 halogen or trifluoromethanesulfonyloxy when X_4 is an ethynyl group), or
23 an activated carboxylic acid function (when X_4 is OH or NH_2). The X_5
24 group can also be an OH, SH or NH_2 group when the X_4 group is an
25 activated carboxylic acid function. Specific examples for substituted
26 phenyl, substituted tetrahydronaphthalene, substituted chroman,
27 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline intermediates
28 having an X_5 functionality are provided below, and are also available in the

1 chemical scientific and patent literature. Generally speaking, for reagents
2 and reactions covalently joining a substituted tetrahydronaphthalene,
3 substituted chroman, thiochroman, or tetrahydroquinoline intermediate with
4 a substituted aryl or heteroaryl group, such as $X_4-A(R_2)-(CH_2)_n-COOR_8$, to
5 form a compound including the linker designated Z, reference is made to
6 United States Patent Nos. 5,648,503; 5,723,666 and 5,952,345 the
7 specification of each of which are expressly incorporated herein by
8 reference.

9 The substituted phenyl, tetrahydronaphthalene, chroman,
10 thiochroman, tetrahydroquinoline or tetrahydroisoquinoline moiety of the
11 novel compounds of the invention are derivatized in a manner to include the
12 specific substituents (such as for example the cycloalkyl substituents)
13 encompassed within the scope of the invention, either before or after the -
14 $A(R_2)-(CH_2)_n-COOR_8$ moiety has been attached and the linker Z has
15 formed, as illustrated by the below described specific examples.
16 The $-(CH_2)_n-COOR_8$ moiety of the compounds of the invention can be
17 modified in order to obtain still further compounds of the invention. One
18 such modification is saponification of compounds where the R_8 group is an
19 alkyl or $-CH_2O(C_{1-6}\text{-alkyl})$ group. Another modification is esterification of
20 the carboxylic acid function when the R_8 group is H or a cation. Such
21 saponification and esterification reactions are well known in the art and
22 within the skill of the practicing organic chemist. Still another modification
23 of the compounds of the invention (or of the intermediates $X_4-A(R_2)-$
24 $CH_2)_n-COOR_8$, or of precursors to these intermediates) is the
25 homologation of the $(CH_2)_n$ group. The latter can be accomplished, for
26 example, by the well known *Arndt-Eistert* method of homologation, or other
27 known methods of homologation.

SPECIFIC EMBODIMENTS

With reference to the symbol A in Formulas 1 through 8, the preferred compounds of the invention are those where A is phenyl, naphthyl, pyridyl, thienyl or furyl. Even more preferred are compounds where A is phenyl. As far as substitutions on the A (phenyl) and A (pyridyl) groups are concerned, compounds are preferred where the phenyl group is 1,4 (*para*) substituted and where the pyridine ring is 2,5 substituted. (Substitution in the 2,5 positions in the "pyridine" nomenclature corresponds to substitution in the 6-position in the "nicotinic acid" nomenclature.) In the presently preferred compounds of the invention either there is no R₂ substituent on the A group, or the R₂ substituent is preferably a fluoro group that is preferably located on the aromatic carbon adjacent (*ortho*) to the carbon bearing the -(CH₂)_n-COOR₈ group.

As far as the -(CH₂)_n-COOR₈ is concerned compounds are preferred where n is 0, 1 or 2, and even more preferred where n is 1. In Formulas 5 and 8 only compounds where n is 1 or 2 are preferred, with n=1 being most preferred. For the R₈ group H, lower alkyl of 1 to 3 carbons, and -CH₂O(C₁₋₆-alkyl) groups are preferred, as well as the pharmaceutically acceptable salts of the free acids when R₈ is H. Among the lower alkyl and -CH₂O(C₁₋₆-alkyl) groups ethyl and OCH₂CH₃, respectively, are presently most preferred.

The linker group Z in all the compounds of the invention is preferably ethynyl (-C≡C-), ester (CO-O), ethenyl, (-CR₁=CR₁-) or amide (CONR₁). Among these the ethynyl (-C≡C-) and ester (CO-O) linkers are most preferred. Moreover, in the preferred compounds of the invention the linker Z is attached to the 6 position in Formula 1, to the 4 position in Formula 2,

1 to the 6 position in **Formula 3**, to the 6 position in **Formula 4**, to the 4
2 position in **Formula 5**, to the 4 position in **Formula 6**, to the 6 position in
3 **Formula 7**, and to the 6 position in **Formula 8**. These positions are
4 indicated by arabic numerals in **Formulas 1** through **8**.

5 The R_1 group substituting the non-aromatic rings in **Formulas 1, 3,**
6 **4, 7 and 8** is preferably alkyl, more preferably alkyl of 1 to 3 carbons, and
7 most preferably methyl. The R_1 group substituting the cyclopropane ring in
8 **Formulas 1, 2, 3 and 7** is preferably non-existent (p is 0), or is alkyl of 1 to
9 3 carbons, even more preferably methyl.

10 The X group in **Formulas 1 and 5** is preferably O, and in **Formula 2**
11 X is preferably O or NR.

12 The X_1 group in **Formula 4** is preferably 1-imidazolyl, substituted 1-
13 imidazolyl, or NRR_6 , where R_6 is preferably cyclopropyl or branched-chain
14 alkyl. The X_2 group in **Formula 6** is preferably 1-imidazolyl or substituted
15 1-imidazolyl.

16 The X_3 group in **Formula 8** is preferably O or C=O.

17 The Y group is preferably H, lower alkyl of 1 to 3 carbons,
18 cycloalkyl, lower alkyl substituted cycloalkyl, or halogen. Among these, H,
19 Cl, and cyclopropyl are most preferred.

20 The Y_1 group of **Formula 8** is preferably H, lower alkyl of 1 to 3
21 carbons, cycloalkyl, or lower alkyl substituted cycloalkyl. Among these H,
22 ethyl and cyclopropyl are presently most preferred.

23 The most preferred compounds of the invention are disclosed in
24 **Tables 2** through **9** with reference to **Formulas 9** through **16**. The
25 compounds specifically shown in **Tables 2** through **9** are carboxylic acids,
26 but it should be understood that the C_{1-3} alkyl esters, methoxymethyl
27 (OCH_2CH_3) esters and pharmaceutically acceptable salts of the acids shown

1 in these tables are also highly preferred.

2 It should also be apparent that the preferred compounds shown in
3 **Table 2** with reference to the more specific **Formula 9** are within the scope
4 of **Formula 1**.

5 Similarly, the preferred compounds shown in **Table 3** with reference
6 to the more specific **Formula 10** are within the scope of **Formula 2**;

7 the preferred compounds shown in **Table 4** with reference to the
8 more specific **Formula 11** are within the scope of **Formula 3**;

9 the preferred compounds shown in **Table 5** with reference to the
10 more specific **Formula 12** are within the scope of **Formula 4**;

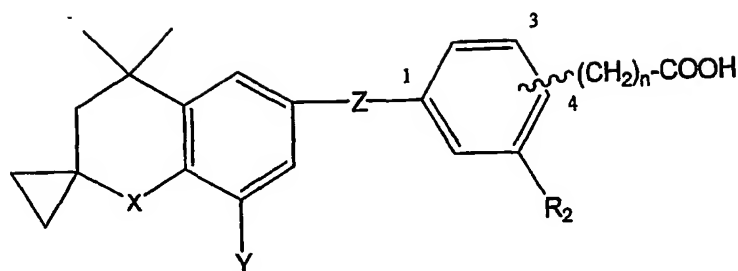
11 the preferred compounds shown in **Table 6** with reference to the
12 more specific **Formula 13** are within the scope of **Formula 5**;

13 the preferred compounds shown in **Table 7** with reference to the
14 more specific **Formula 14** are within the scope of **Formula 6**;

15 the preferred compounds shown in **Table 8** with reference to the
16 more specific **Formula 15** are within the scope of **Formula 7**, and

17 the preferred compounds shown in **Table 9** with reference to the
18 more specific **Formula 16** are within the scope of **Formula 8**.

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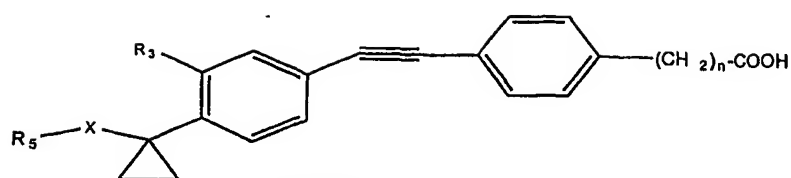


Formula 9

TABLE 2

Compound No.	X	Y	Z	R ₂	n	Position of (CH ₂) _n COOH
40	O	H	-C≡C-	H	0	4
42	O	H	-C≡C-	H	1	4
44	O	H	-C≡C-	F	0	4
48	O	cyclopropyl	-C≡C-	H	1	4
50	O	cyclopropyl	-C≡C-	F	1	4
52	O	cyclopropyl	-C≡C-	H	0	4
54	O	cyclopropyl	-C≡C-	F	0	4
58	O	cyclopropyl	-CO-O-	H	1	4
60	O	cyclopropyl	-CO-O-	H	1	3
66	CH ₃ N	H	-C≡C-	H	0	4

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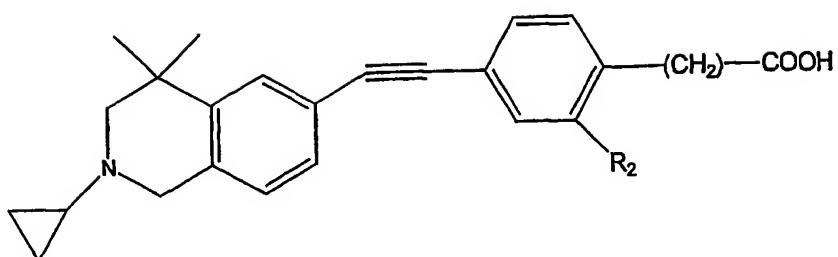


Formula 10

TABLE 3

Compound No.	R_5	X	R_3	n
110	n-propyl	(n-propyl)N	H	0
112	benzyl	NH	H	0
114	benzyl	(n-benzyl)N	H	0
108	n-propyl	NH	H	0
116	benzyl	methylN	H	0
77	benzyl	O	H	0
78	benzyl	O	H	1
70	methyl	O	H	1
69	methyl	O	H	0
73	isopropyl	O	H	0
74	isopropyl	O	H	1
82	benzyl	O	methyl	1
81	benzyl	O	methyl	0
89	$(CH_3)_3C-CH_2-$	O	methyl	0
90	$(CH_3)_3C-CH_2-$	O	methyl	1
94	benzyl	O	ethyl	1
93	benzyl	O	ethyl	0
86	isopropyl	O	methyl	1
85	isopropyl	O	methyl	0
105	ethyl	O	<i>t</i> -butyl	0
106	ethyl	O	<i>t</i> -butyl	1
98	isopropyl	O	ethyl	1

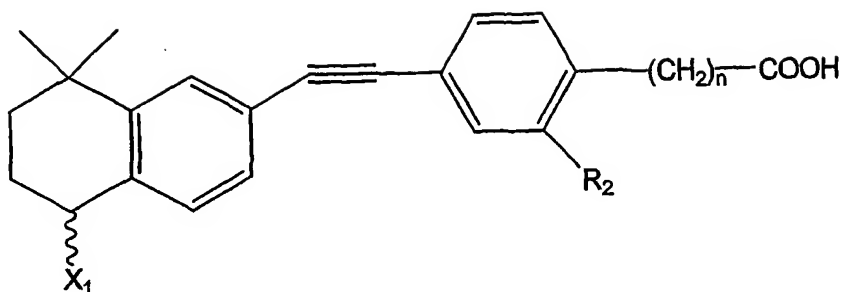
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Formula 11

TABLE 4

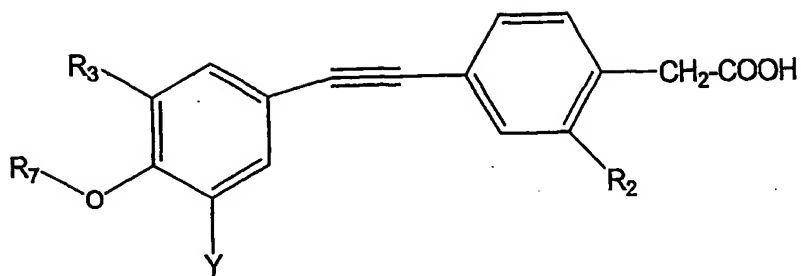
Compound No.	R_2
22	F
24	H



Formula 12

TABLE 5

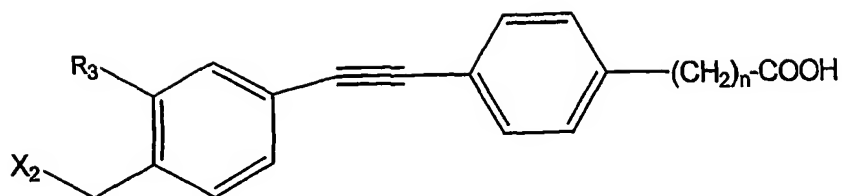
Compound No.	X_1	R_2	n
3	methyl,cyclopropyl-N	H	0
8	methyl,cyclopropyl-N	H	1
13	methyl,cyclopropyl-N	F	0
18	methyl,cyclopropyl-N	F	1
139	1-imidazolyl	H	0
137	1-imidazolyl	H	1
26	methyl,isopropyl-N	H	0



Formula 13

TABLE 6

Compound No.	R_2	R_7	Y	R_3
143	H	methyl	<i>t</i> -butyl	<i>t</i> -butyl
145	F	methyl	<i>t</i> -butyl	<i>t</i> -butyl

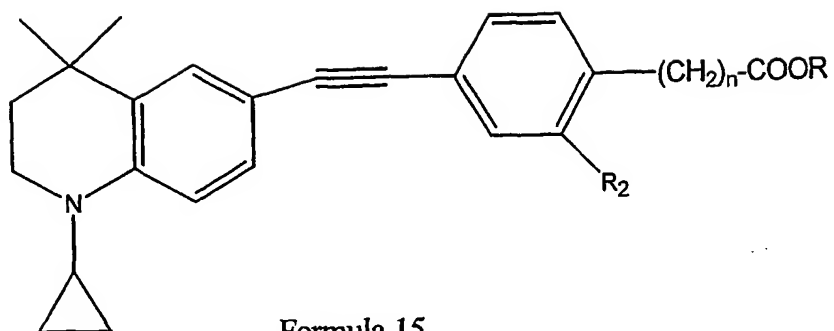


Formula 14

TABLE 7

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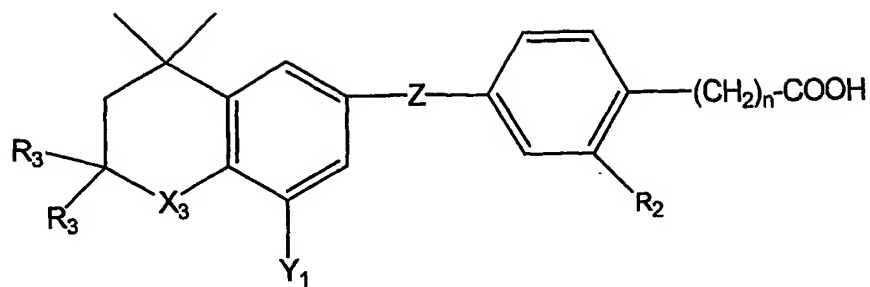
Compound No.	X_2	R_3	n
119	1-imidazolyl	methyl	0
121	1-imidazolyl	methyl	1
127	1-imidazolyl	iso-propyl	1
126	1-imidazolyl	iso-propyl	0
134	ethyl,cyclopropyl-N	iso-propyl	0
130	ethyl,cyclopropyl-N	methyl	0
131	ethyl,cyclopropyl-N	methyl	1
141	(1-methyl)cyclopropyl-oxy	iso-propyl	1



Formula 15

TABLE 8

Compound No.	R	R ₂	n
62	H	H	0
63	Me	H	1



Formula 16

TABLE 9

Compound No.	X ₃	Y ₁	R ₃	Z	R ₂	n
28	O	H	methyl	-C≡C-	H	1
30	O	H	methyl	-C≡C-	F	0
5	CO	H	H	-C≡C-	H	1
10	CO	H	H	-C≡C-	F	0
36	O	cyclopropyl	methyl	-C≡C-	H	1
38	O	cyclopropyl	methyl	-C≡C-	F	1
46	O	H	methyl	-CO-O-	H	1
20	CO	H	H	-CO-O-	H	1
32	O	H	methyl	-C≡C-	F	1
56	O	ethyl	methyl	-C≡C-	H	1
34	O	cyclopropyl	methyl	-C≡C-	H	0
15	CO	H	H	-C≡C-	F	1

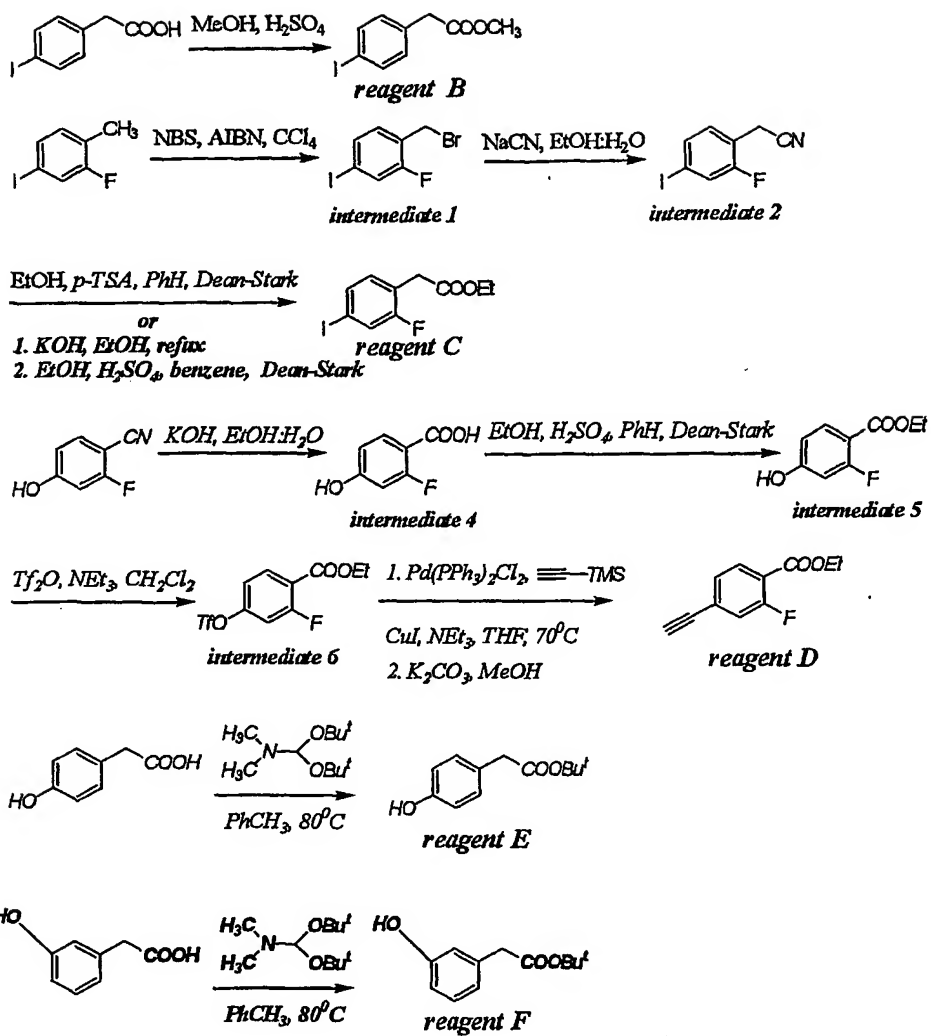
1 The compounds of the invention can be synthesized by applying the
2 general synthetic methodology described above, and by such modifications
3 of the hereinafter described specific synthetic routes which will become
4 readily apparent to the practicing synthetic organic chemist in light of this
5 disclosure and in view of general knowledge available in the art. The
6 hereinafter disclosed specific reaction schemes are directed to the synthesis
7 of exemplary and preferred compounds of the invention. Whereas each of
8 the specific and exemplary synthetic routes shown in these schemes may
9 describe specific compounds of the invention only within the scope of one
10 or two of the general **Formulas 1** through **8**, the synthetic processes and
11 methods used therein are adaptable within the skill of the practicing organic
12 chemist and can be used with such adaptation for the synthesis of
13 compounds of the invention which are not specifically described herein as
14 examples.

15 **Reaction Scheme 1** discloses a presently preferred synthetic route to
16 certain intermediates or reagents having the general formula $X_4-A(R_2)-$
17 $CH_2)_n-COOR_8$, where the symbol A represents a di-, or tri-substituted
18 phenyl moiety. These intermediates are utilized in the synthesis of the
19 compounds of the invention.

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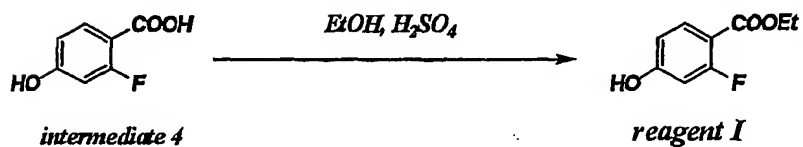
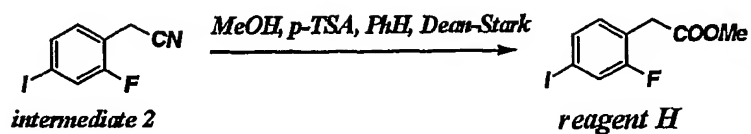
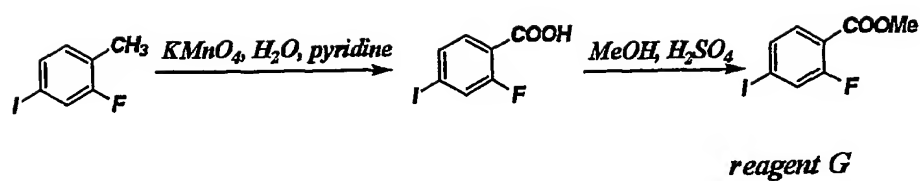


REACTION SCHEME 1

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REACTION SCHEME 1 CONTINUED

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3 **Reaction Scheme 2** discloses presently preferred synthetic routes to
4 obtain exemplary and preferred tetrahydronaphthalenone compounds of the
5 invention within the scope of **Formula 8** where the symbol X_3
6 represents a C=O group, **Z** represents an ethynyl moiety or a -COO- (ester)
7 function, and **A** is a substituted phenyl moiety.

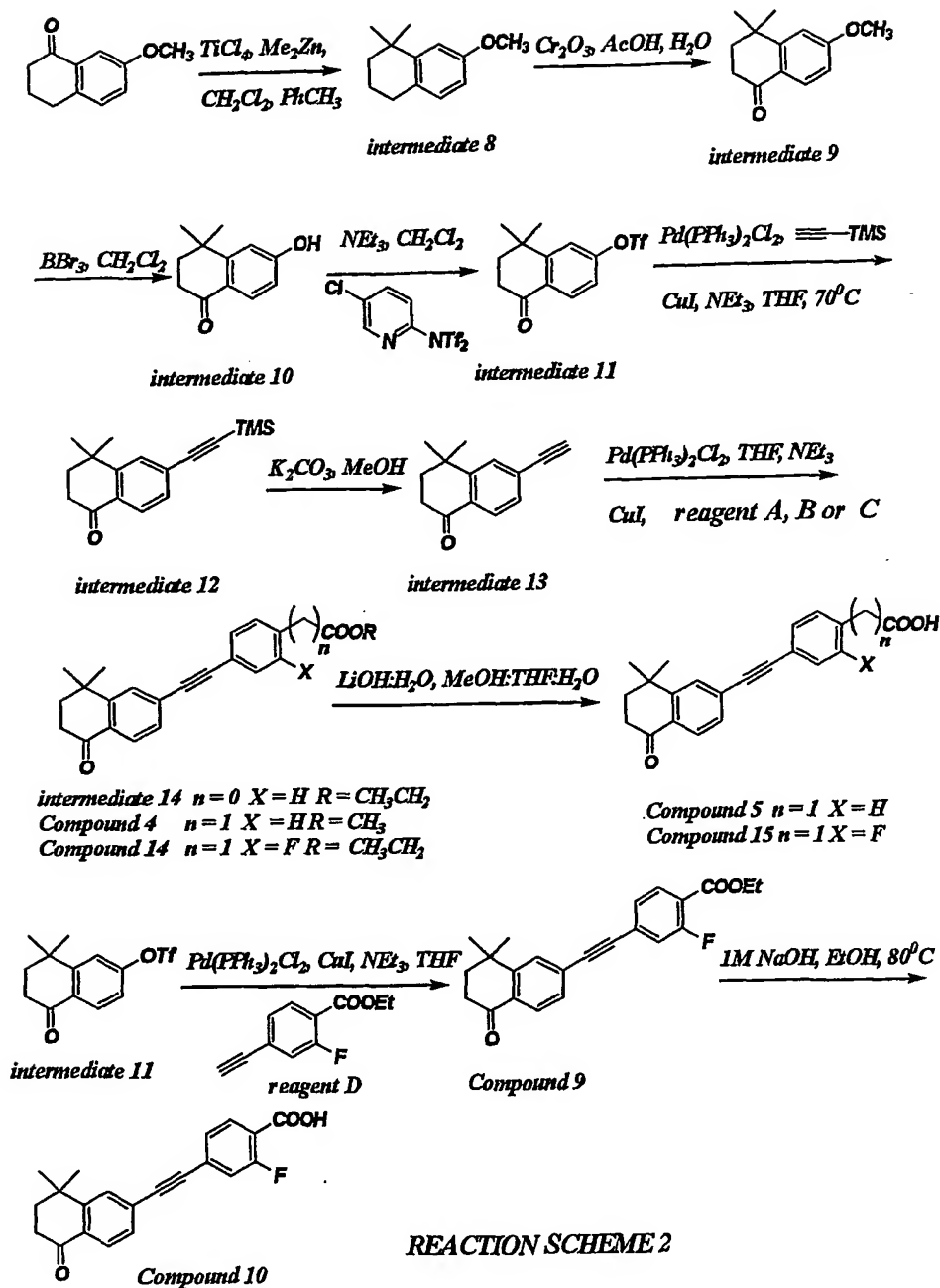
8 **Reaction Scheme 3** discloses presently preferred synthetic routes to
9 obtain exemplary and preferred tetrahydronaphthalene compounds of the
10 invention within the scope of **Formula 4** where X_1 represents a dialkyl
11 substituted nitrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl
12 moiety.

13 **Reaction Scheme 4** discloses presently preferred synthetic routes to
14 obtain exemplary and preferred isoquinoline compounds of the invention
15 within the scope of **Formula 3** where the symbol **Y** represents hydrogen, **Z**
16 is an ethynyl moiety and **A** is a substituted phenyl moiety.

17 **Reaction Scheme 5** discloses presently preferred synthetic routes to
18 obtain exemplary and preferred chroman compounds of the invention within
19 the scope of **Formula 8** where the symbol Y_1 represents hydrogen, **Z** is an
20 ethynyl moiety or an ester (COO) function, and **A** is a substituted phenyl
21 moiety.

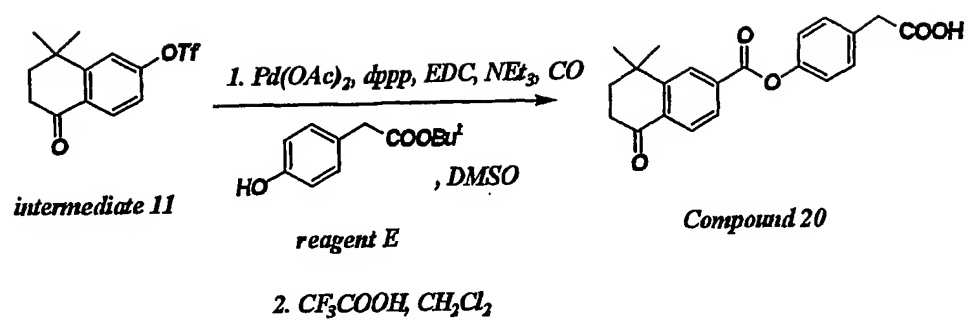
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REACTION SCHEME 2

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**REACTION SCHEME 2 CONTINUED**

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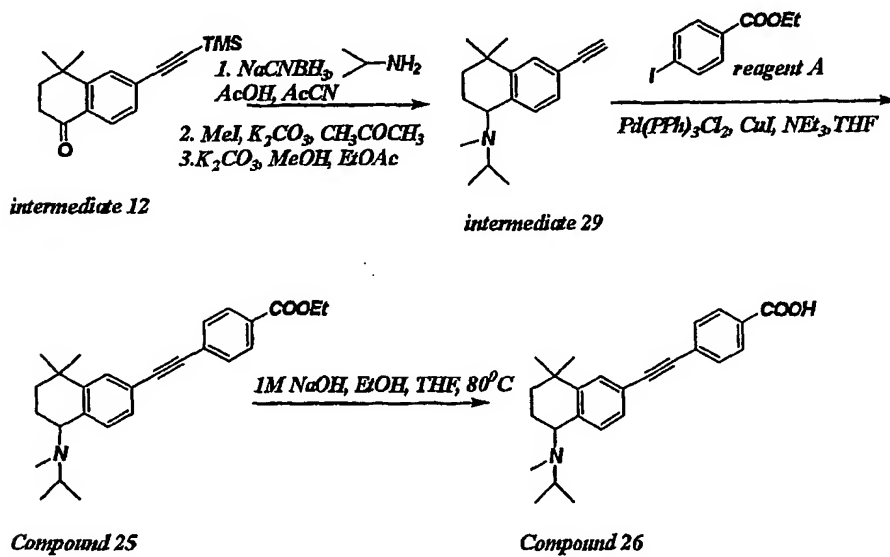
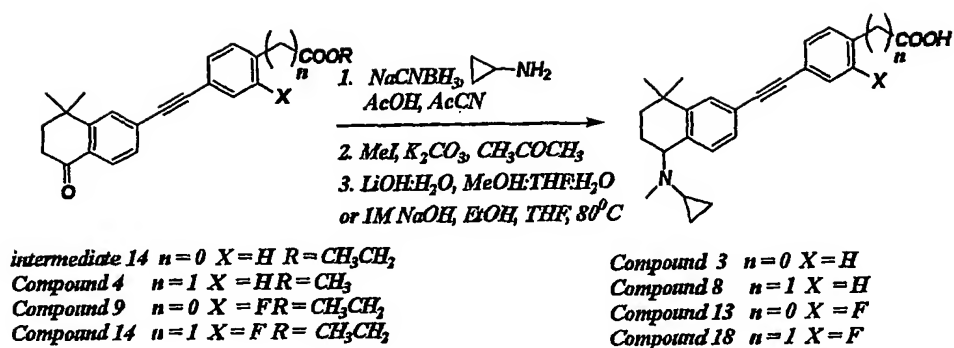
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REACTION SCHEME 3

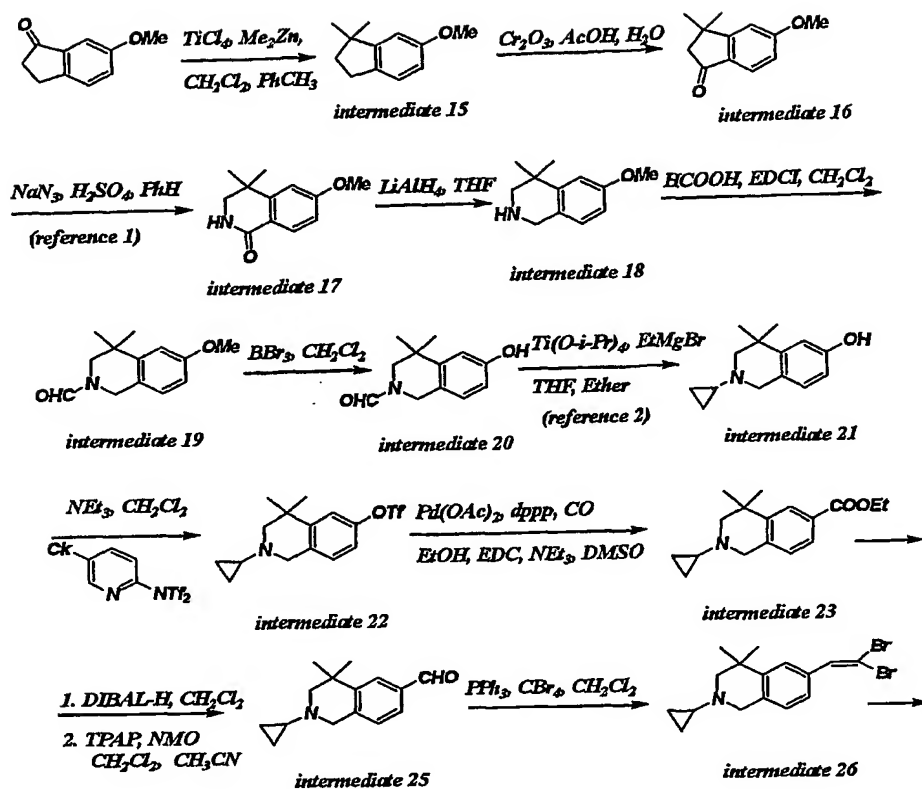
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TPAP = tetra-*n*-propyl ammonium perthenate
 NMO = *N*-methylmorpholine *N*-oxide

reference 1 Tomita et al. *J. Chem. Soc. (c)*, 1969, 183-188

reference 2 Chaplinski et al. *Angew. Chem. Int. Edn. Engl.*, 1996, 35, 413-414

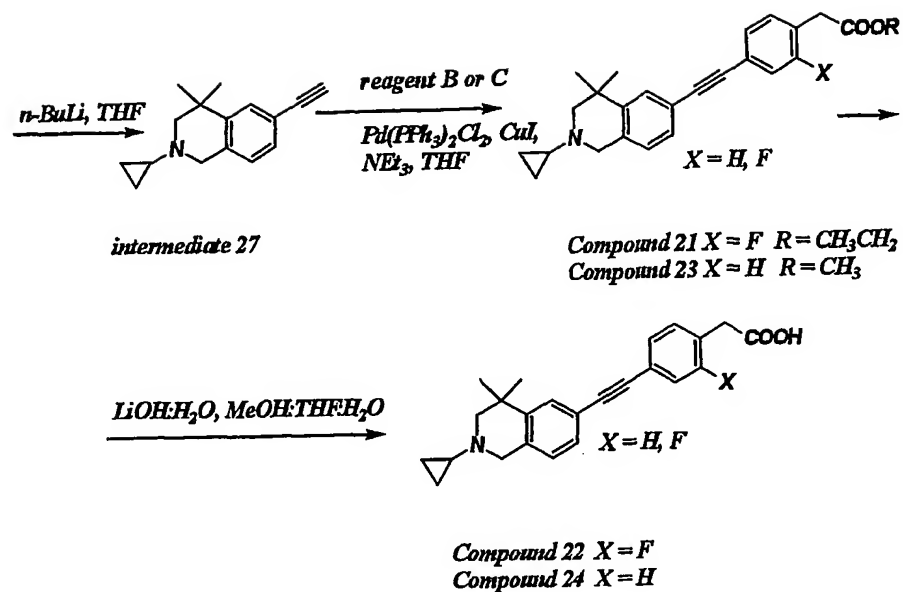
REACTION SCHEME 4

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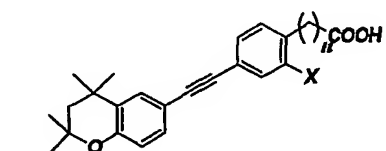
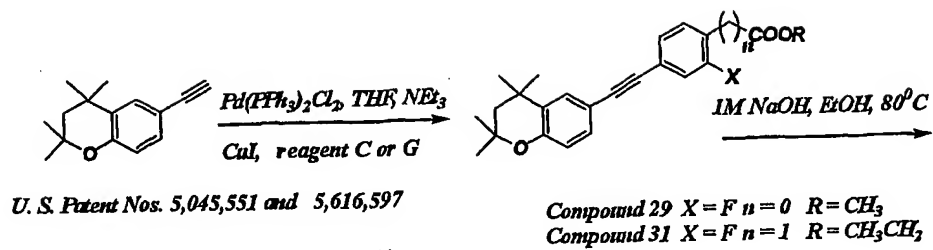
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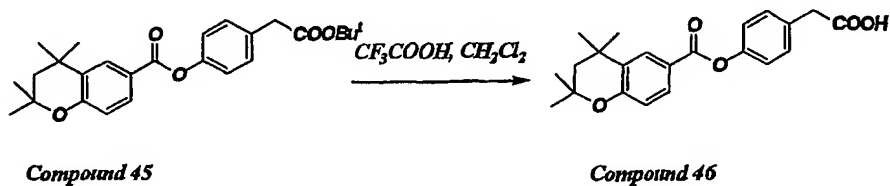
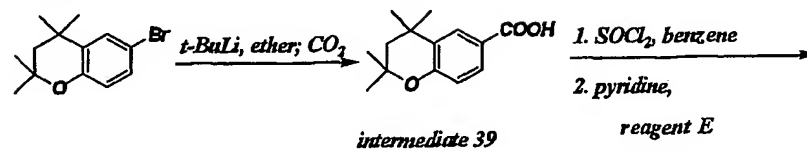
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Compound 30 $X = F$ $n = 0$
 Compound 32 $X = F$ $n = 1$



REACTION SCHEME 5

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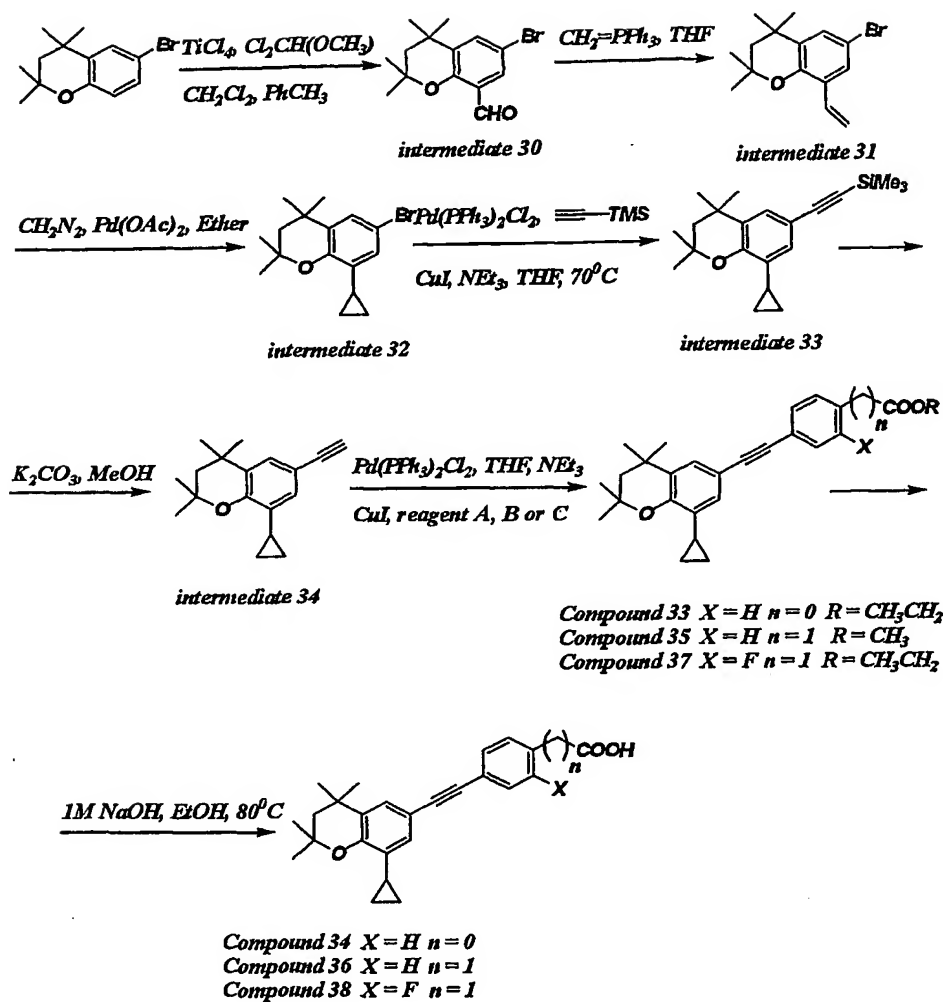
1 **Reaction Scheme 6** discloses presently preferred synthetic routes to
2 obtain other exemplary and preferred chroman compounds of the invention
3 within the scope of **Formula 8** where the symbol Y_1 represents a
4 cyclopropyl group, **Z** is an ethynyl moiety and **A** is a substituted phenyl
5 moiety.

6 **Reaction Scheme 7** discloses presently preferred synthetic routes to
7 obtain exemplary and preferred chroman compounds of the invention within
8 the scope of **Formula 1** where the symbol **X** represents oxygen (O), **Y**
9 represents hydrogen, **Z** is an ethynyl moiety and **A** is a substituted phenyl
10 moiety.

11 **Reaction Scheme 8** discloses presently preferred synthetic routes to
12 obtain other exemplary and preferred chroman compounds of the invention
13 within the scope of **Formula 1** where the symbol **X** represents oxygen (O),
14 **Y** represents a cyclopropyl group, **Z** is an ethynyl moiety and **A** is a
15 substituted phenyl moiety.

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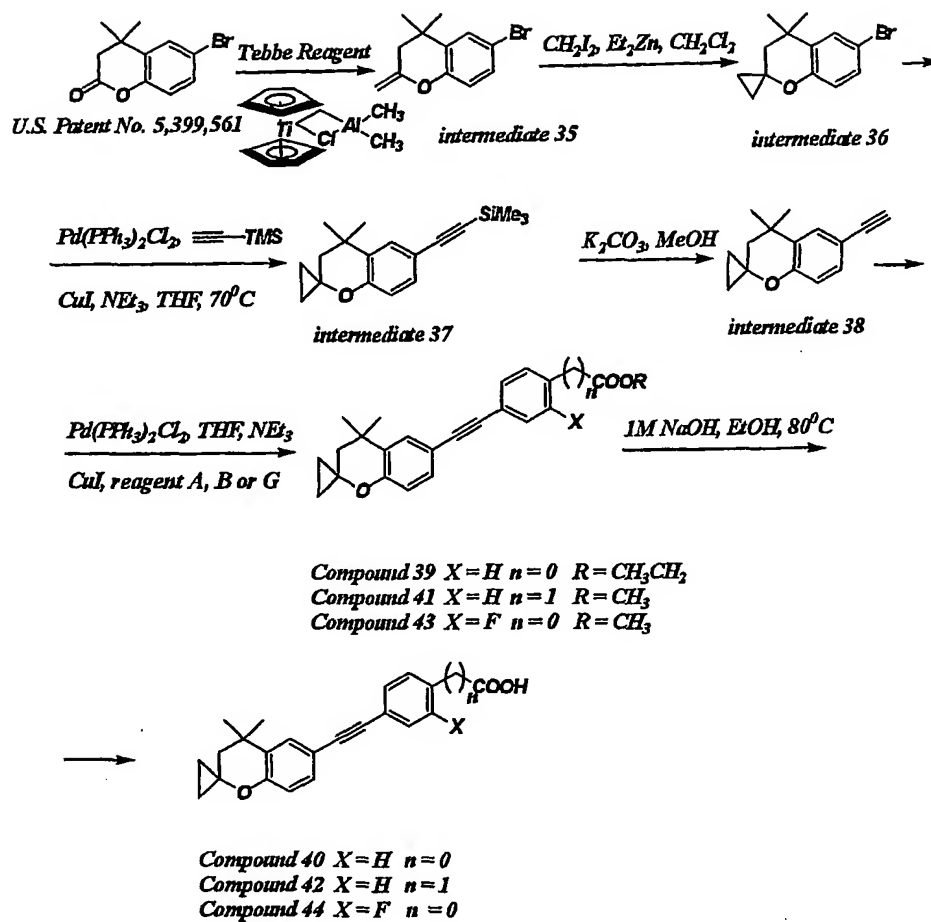


REACTION SCHEME 6

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REACTION SCHEME 7

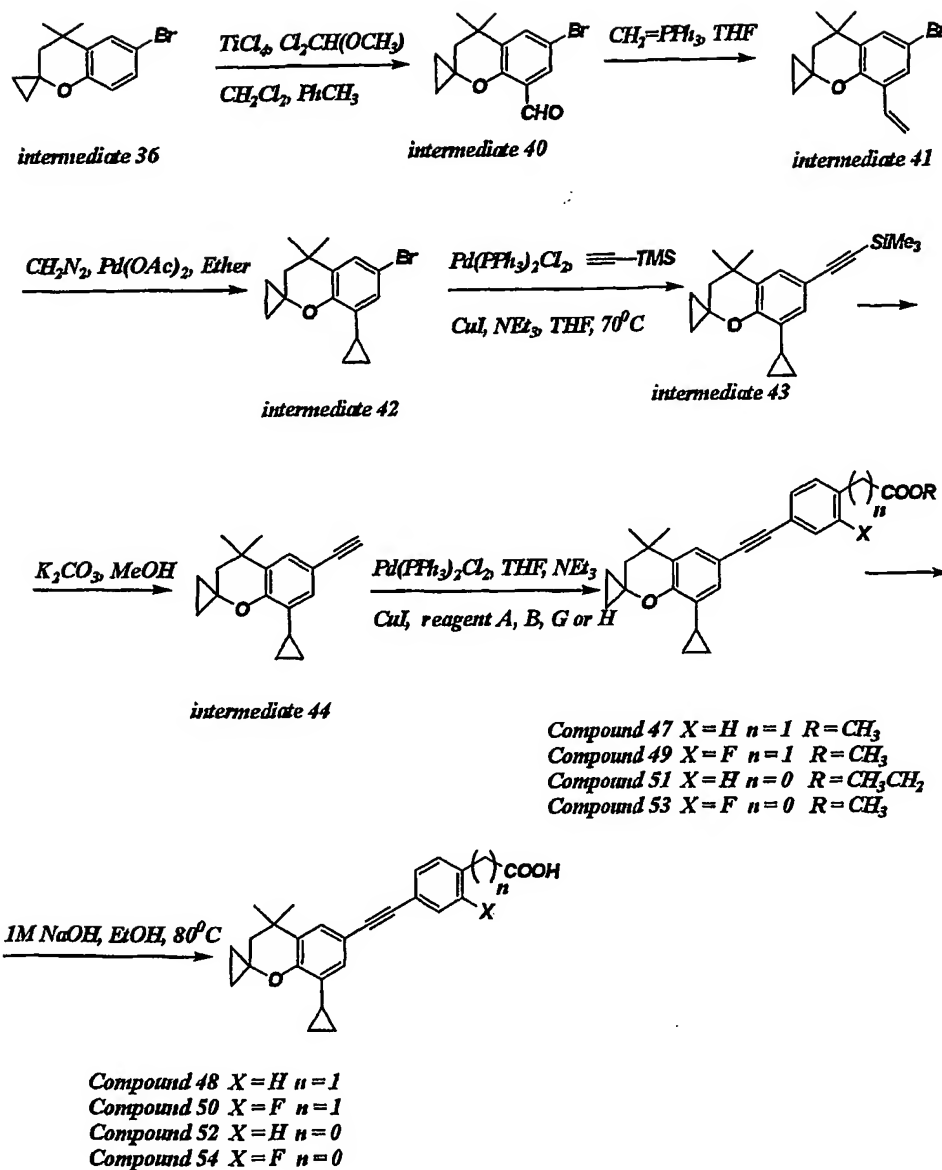
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REACTION SCHEME 8

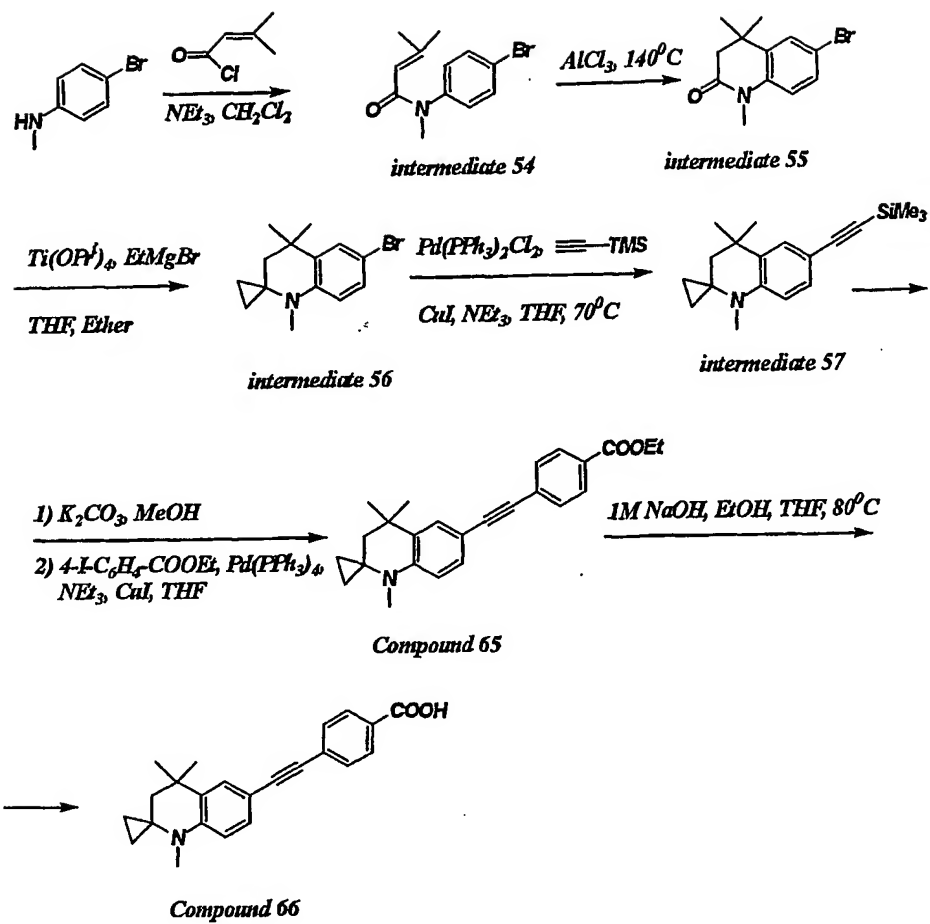
1 **Reaction Scheme 9** discloses presently preferred synthetic routes to
2 obtain exemplary and preferred tetrahydroquinoline compounds of the
3 invention within the scope of **Formula 1** where the symbol **X** represents an
4 alkyl substituted nitrogen (alkyl-N), **Y** represents hydrogen, **Z** is an ethynyl
5 moiety and **A** is a substituted phenyl moiety.

6 **Reaction Schemes 10 and 11** disclose presently preferred synthetic
7 routes to obtain exemplary and preferred phenyl compounds of the invention
8 within the scope of **Formula 2** where the symbol **X** represents oxygen (O),
9 **R₅** is alkyl or benzyl, **Z** is an ethynyl moiety and **A** is a substituted phenyl
10 moiety.

11 **Reaction Scheme 12** discloses presently preferred synthetic routes to
12 obtain exemplary and preferred phenyl compounds of the invention within
13 the scope of **Formula 2** where the symbol **R₅-X** represents an alkyl, dialkyl,
14 benzyl or dibenzyl substituted nitrogen, **Z** is an ethynyl moiety and **A** is a
15 substituted phenyl moiety.

16 **Reaction Schemes 13 and 14** disclose presently preferred synthetic
17 routes to obtain exemplary and preferred phenyl compounds of the invention
18 within the scope of **Formula 6** where the symbol **X₂** represents a (1-
19 imidazolyl) moiety, **Z** is an ethynyl moiety and **A** is a substituted phenyl
20 moiety.

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REACTION SCHEME 9

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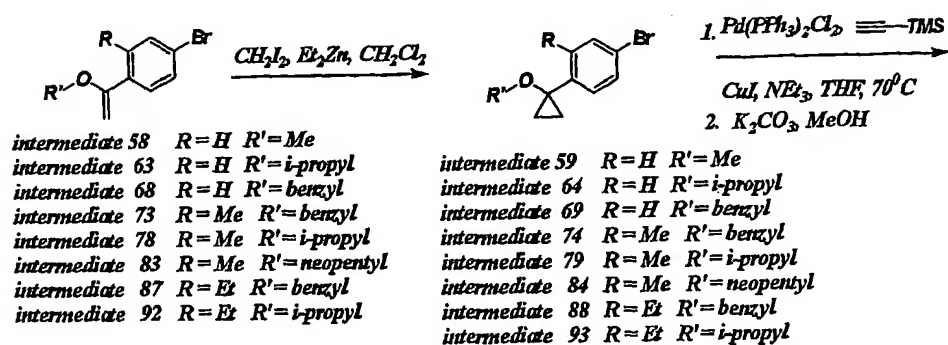
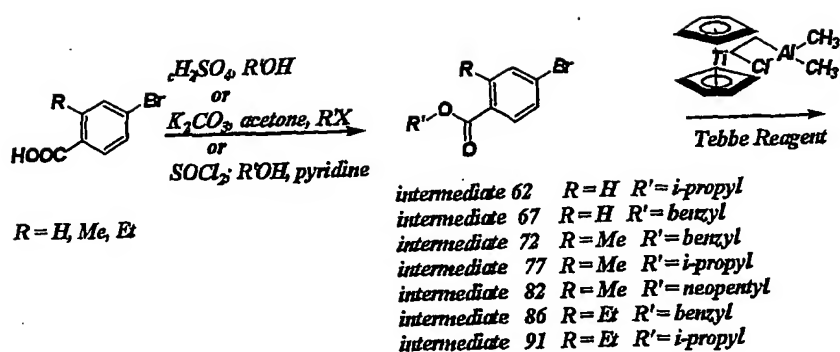
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REACTION SCHEME 10

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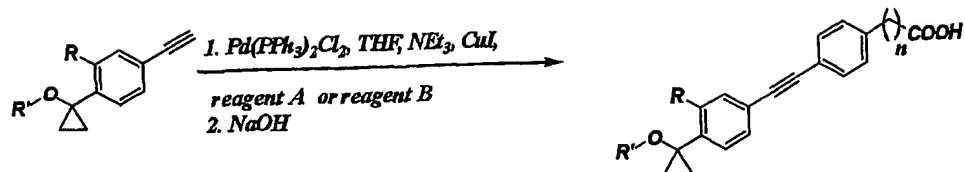
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intermediate 61 $R=\text{H}$ $R'=\text{Me}$
intermediate 66 $R=\text{H}$ $R'=\text{i-propyl}$
intermediate 71 $R=\text{H}$ $R'=\text{benzyl}$
intermediate 76 $R=\text{Me}$ $R'=\text{benzyl}$
intermediate 81 $R=\text{Me}$ $R'=\text{i-propyl}$
intermediate 85 $R=\text{Me}$ $R'=\text{neopentyl}$
intermediate 90 $R=\text{Et}$ $R'=\text{benzyl}$
intermediate 95 $R=\text{Et}$ $R'=\text{i-propyl}$

Compound 69 $n=0$ $R=\text{H}$ $R'=\text{methyl}$
Compound 70 $n=1$ $R=\text{H}$ $R'=\text{methyl}$
Compound 73 $n=0$ $R=\text{H}$ $R'=\text{i-propyl}$
Compound 74 $n=1$ $R=\text{H}$ $R'=\text{i-propyl}$
Compound 77 $n=0$ $R=\text{H}$ $R'=\text{benzyl}$
Compound 78 $n=1$ $R=\text{H}$ $R'=\text{benzyl}$
Compound 81 $n=0$ $R=\text{Me}$ $R'=\text{benzyl}$
Compound 82 $n=1$ $R=\text{Me}$ $R'=\text{benzyl}$
Compound 85 $n=0$ $R=\text{Me}$ $R'=\text{i-propyl}$
Compound 86 $n=1$ $R=\text{Me}$ $R'=\text{i-propyl}$
Compound 89 $n=0$ $R=\text{Me}$ $R'=\text{neopentyl}$
Compound 90 $n=1$ $R=\text{Me}$ $R'=\text{neopentyl}$
Compound 93 $n=0$ $R=\text{Et}$ $R'=\text{benzyl}$
Compound 94 $n=1$ $R=\text{Et}$ $R'=\text{benzyl}$
Compound 97 $n=0$ $R=\text{Et}$ $R'=\text{i-propyl}$
Compound 98 $n=1$ $R=\text{Et}$ $R'=\text{i-propyl}$

REACTION SCHEME 10 CONTINUED

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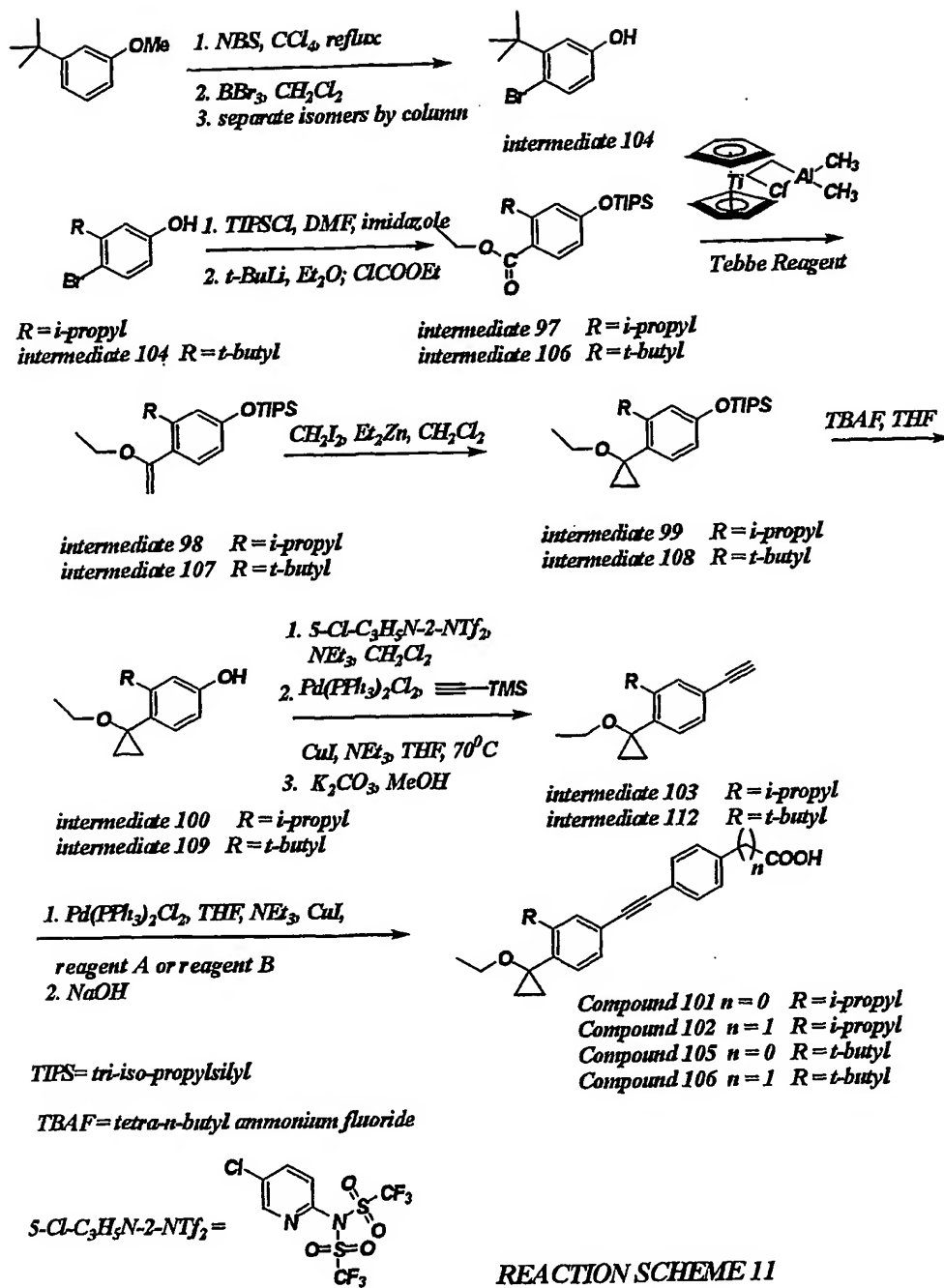
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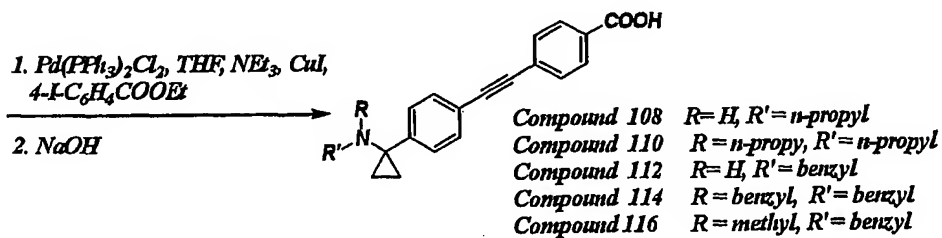
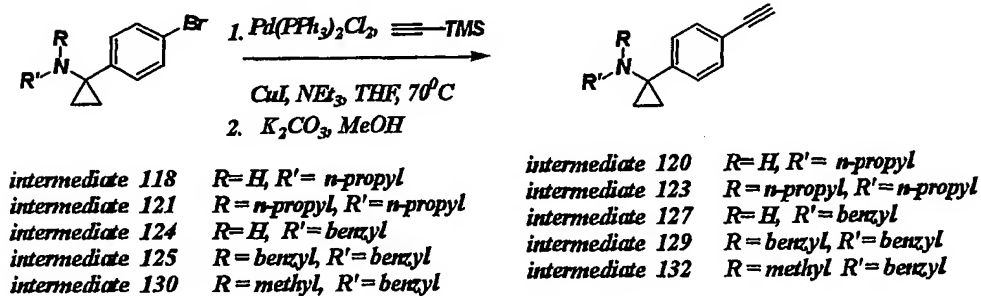
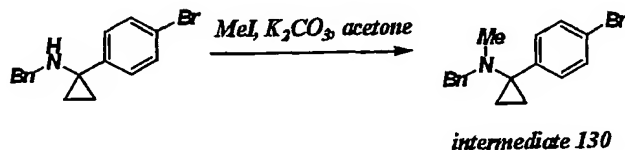
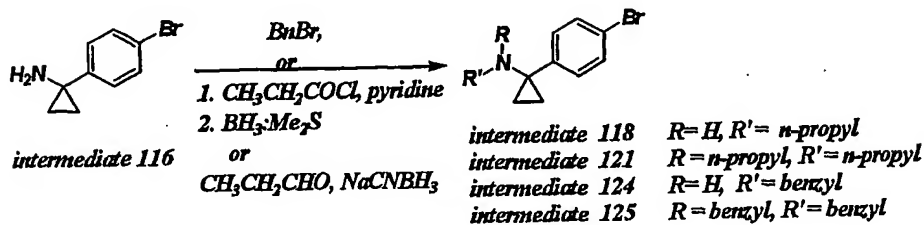
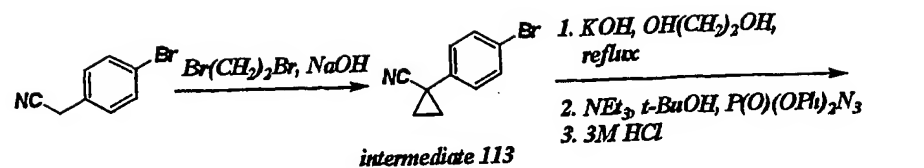
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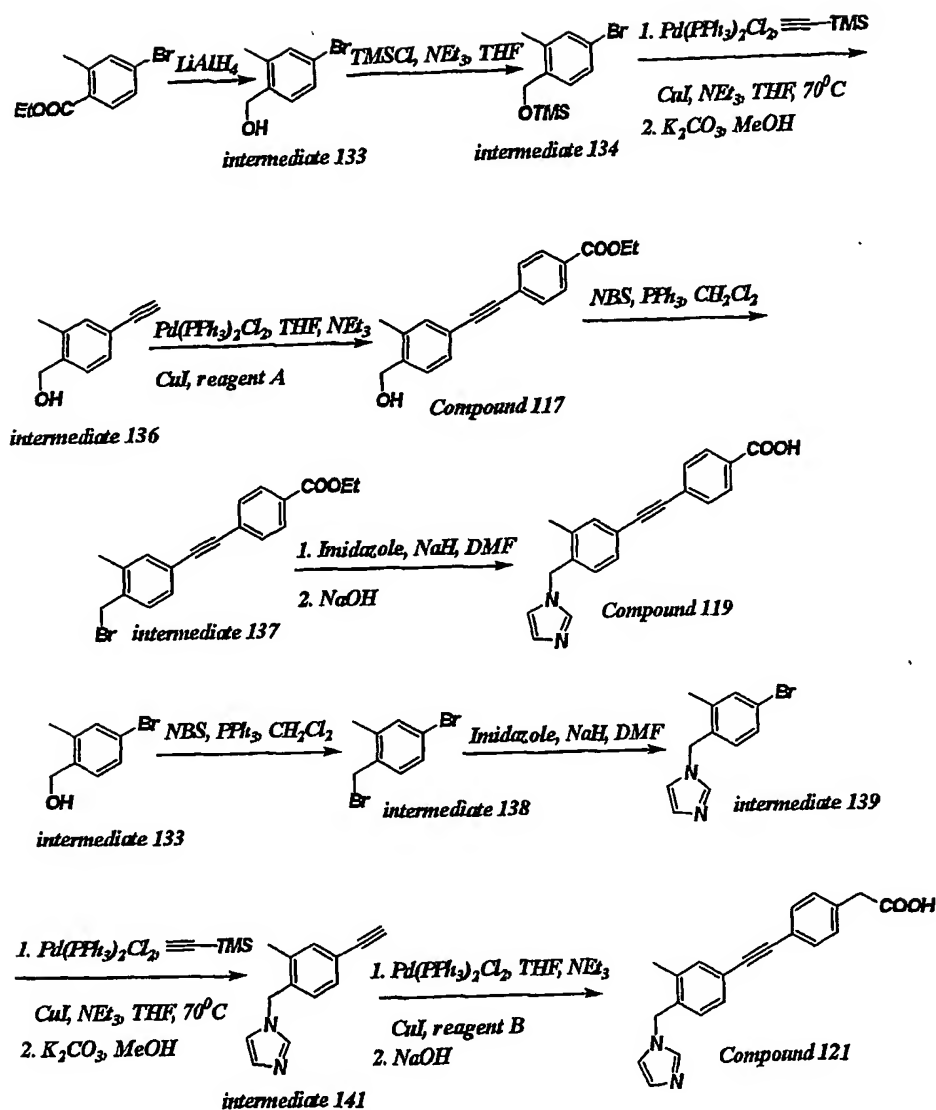
REACTION SCHEME 11



REACTION SCHEME 12

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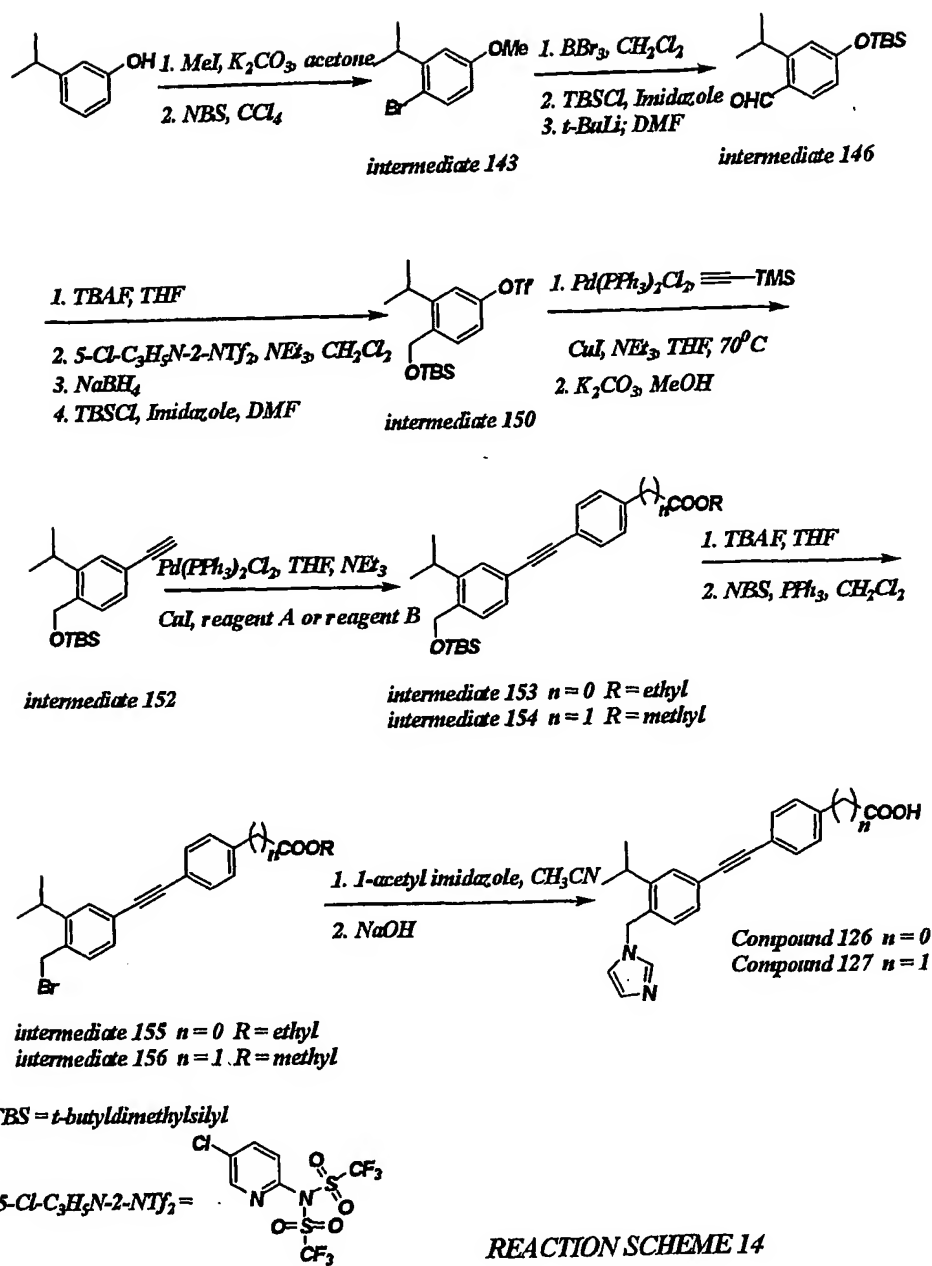
REACTION SCHEME 13

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REACTION SCHEME 14

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1 **Reaction Scheme 15** disclose presently preferred synthetic routes to
2 obtain exemplary and preferred phenyl compounds of the invention within
3 the scope of **Formula 6** where X_2 represents an alkyl and cyclopropyl
4 substituted nitrogen ($X_2 = (\text{alkyl, cycloalkyl})N$), Y represents hydrogen, Z
5 is an ethynyl moiety and A is a substituted phenyl moiety.

6 **Reaction Scheme 16** discloses presently preferred synthetic routes to
7 obtain exemplary and preferred tetrahydronaphthalene compounds of the
8 invention within the scope of **Formula 4** where the symbol X_1 represents a
9 (1-imidazolyl) moiety, Y represents hydrogen, Z is an ethynyl moiety and A
10 is a substituted phenyl moiety.

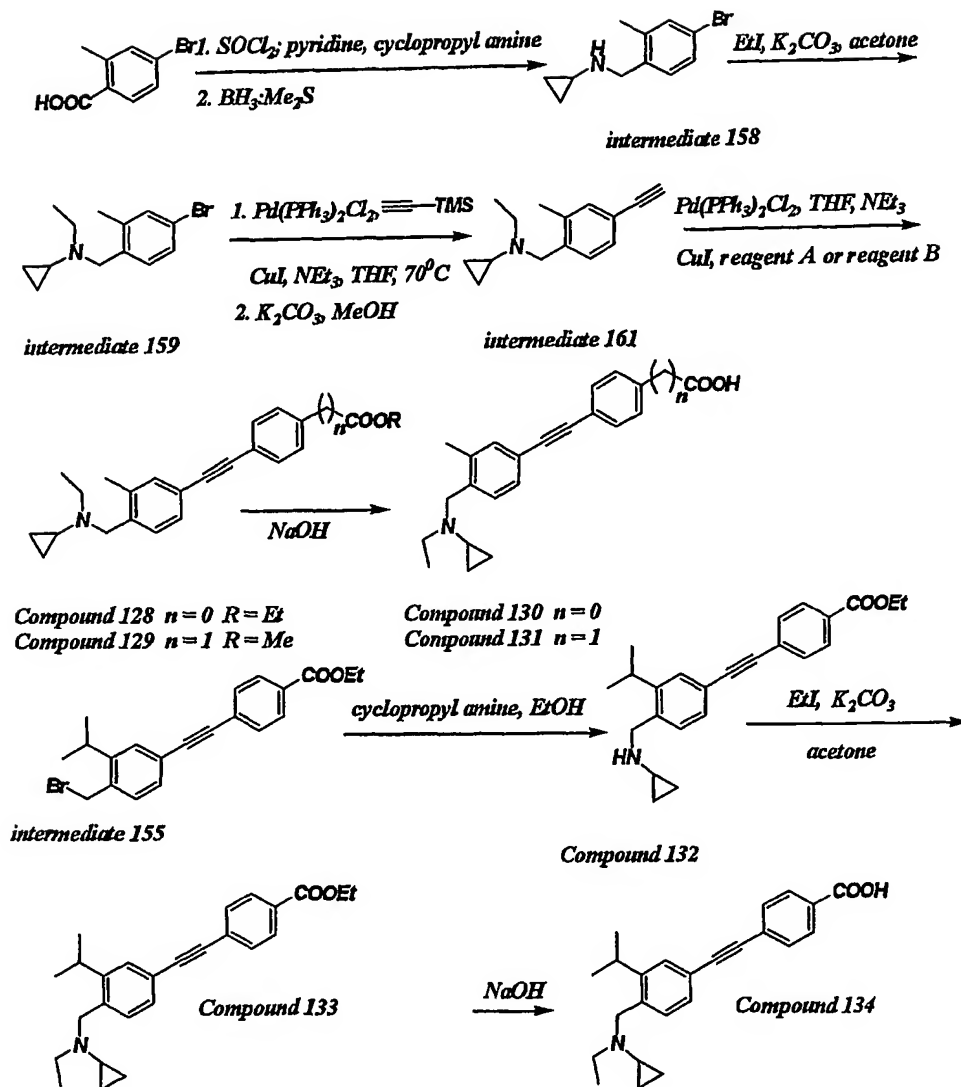
11 **Reaction Scheme 17** discloses presently preferred synthetic routes to
12 obtain exemplary and preferred phenyl compounds of the invention within
13 the scope of **Formula 6** where the symbol X_2 represents a 1-methyl-
14 cyclopropoxy moiety, Y represents hydrogen, Z is an ethynyl moiety and A
15 is a substituted phenyl moiety.

16 **Reaction Scheme 18** discloses presently preferred synthetic routes to
17 obtain exemplary and preferred phenyl compounds of the invention within
18 the scope of **Formula 5** where the symbol X represents oxygen (O), Y
19 represents a *tertiary*-butyl group, Z is an ethynyl moiety and A is a
20 substituted phenyl moiety.

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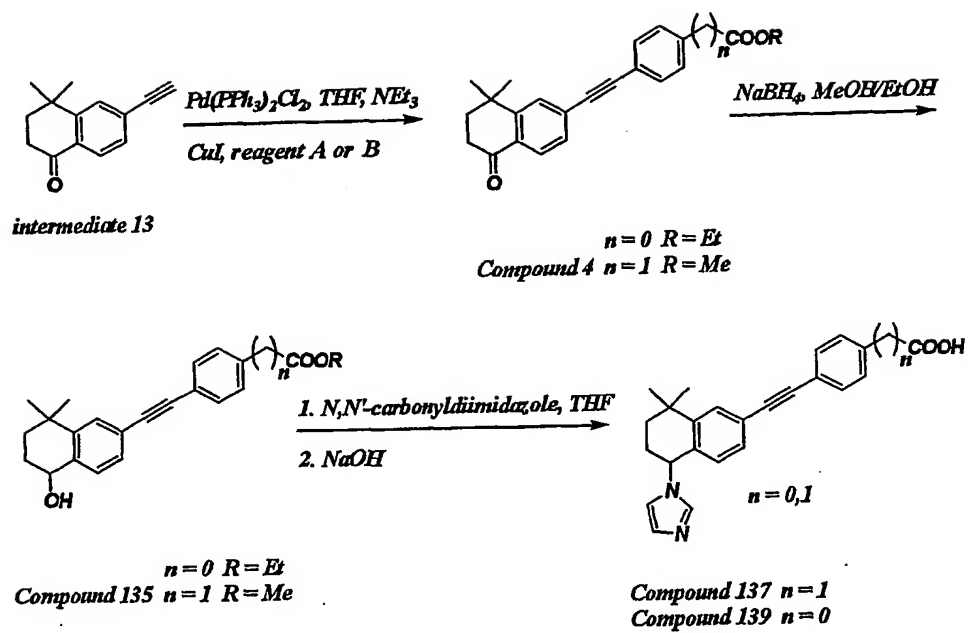


REACTION SCHEME 15

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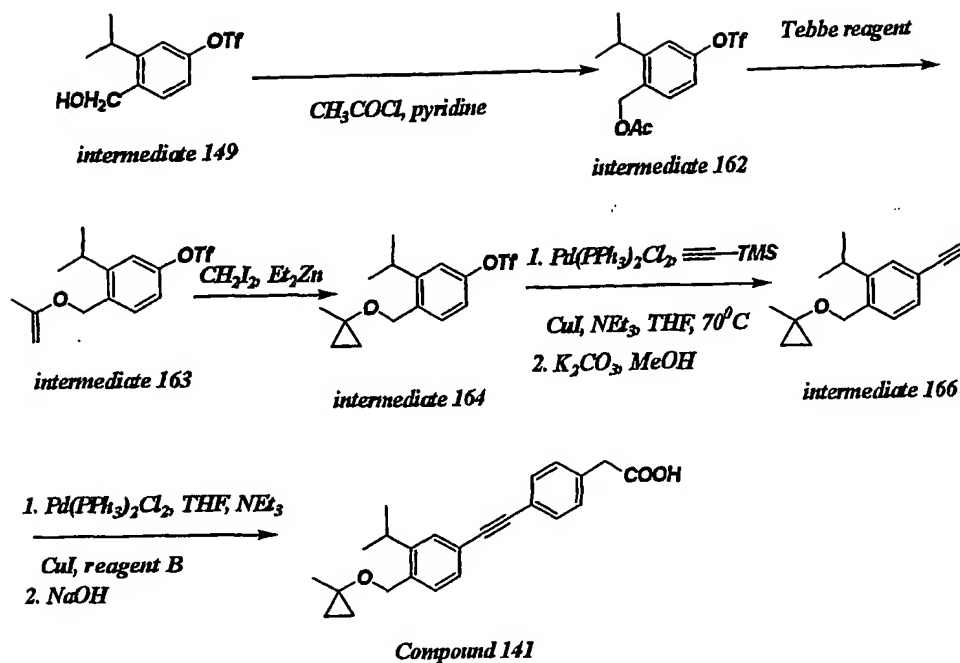
REACTION SCHEME 16

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REACTION SCHEME 17

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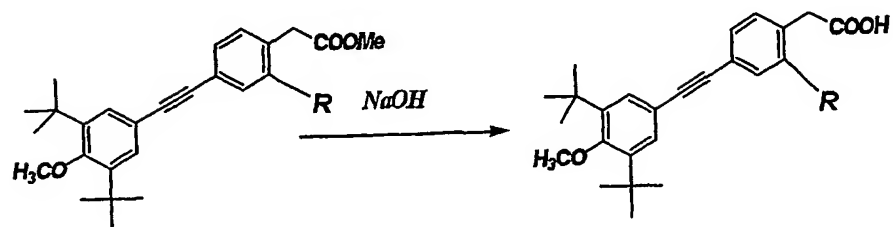
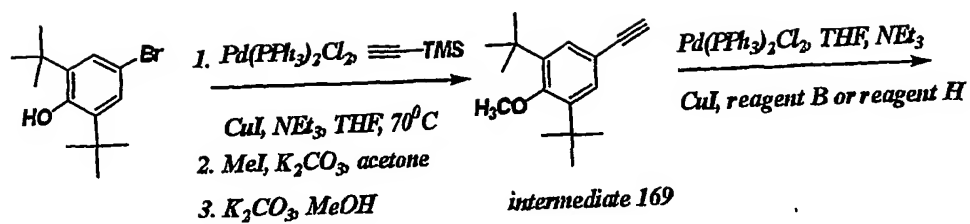
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Compound 142 R=H
Compound 144 R=F

Compound 143 R=H
Compound 145 R=F

REACTION SCHEME 18

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SPECIFIC EXAMPLES

2 4-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent E)

3 A stirred suspension of 4-hydroxy-phenyl acetic acid (0.152g,
4 1mmol) in anhydrous toluene (5mL) was heated at 80°C and N,N-dimethyl
5 formamide-di-*t*-butyl acetal (1mL, 4.17mmol) was added when the solution
6 became homogenous. After 0.5h, the reaction mixture was cooled to
7 ambient temperature and the volatiles were distilled off in *vacuo*. The
8 residue was diluted with water and extracted with diethyl ether (x2). The
9 combined organic extract was dried over anhydrous sodium sulfate, filtered
10 and evaporated in *vacuo* to afford an oil which was subjected to flash
11 column chromatography over silica gel (230-400 mesh) using 16% ethyl
12 acetate in hexane as the eluent to afford the title compound as a solid (0.11g,
13 56%).

14 ¹H-NMR (300 MHz, CDCl₃): δ 1.44(s, 9H), 3.45(s, 2H), 6.55(s, 1H), 6.69(d,
15 *J* = 8.8Hz, 2H), 7.06(d, *J* = 8.5Hz, 2H).

16 3-Hydroxy phenyl acetic acid-*t*-butyl ester (Reagent F)

A stirred suspension of 3-hydroxy-phenyl acetic acid (1.52g, 10mmol) in anhydrous toluene (20mL) was heated at 80°C and N,N-dimethyl formamide-di-*t*-butyl acetal (9.6mL, 40mmol) was added when the solution became homogenous. After 0.5h, the reaction mixture was cooled to ambient temperature and the volatiles were distilled off in *vacuo*. The residue was diluted with water and extracted with diethyl ether (x2). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil which was subjected to flash column chromatography over silica gel (230-400 mesh) using 16% ethyl acetate in hexane as the eluent to afford the title compound as a solid (1.17g, 56%).

1 ¹H-NMR (300 MHz, CDCl₃): δ 1.47(s, 9H), 3.49(s, 2H), 6.30(s, 1H), 6.70-
2 6.79 (m, 2H), 6.81(d, *J* = 7.6Hz, 1H), 7.16(t, *J* = 7.7Hz, 1H).

3 Methyl-2-fluoro-4-iodo benzoate (Reagent G)

4 A solution of 2-fluoro-4-iodo toluene (5g, 26.6mmol) in pyridine
5 (2mL) and water (20mL) was treated with potassium permanganate (16.6g,
6 105mmol) and heated at 150°C overnight. The reaction mixture was then
7 cooled to room temperature and filtered and the filtrate was extracted with
8 hexane. The aqueous phase was acidified with 10% hydrochloric acid and
9 extracted with ethyl acetate. The organic phase was dried over anhydrous
10 sodium sulfate, filtered and evaporated in *vacuo*. The residue was dissolved
11 in 20mL of methanol, treated with concentrated sulfuric acid (1mL) and
12 refluxed overnight. The volatiles were distilled off in *vacuo* and the residue
13 was dissolved in diethyl ether, washed with brine, dried over anhydrous
14 sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash column
15 chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in
16 hexane as the eluent afforded the title compound as an oil (0.26g, 5%).
17 ¹H NMR (300 MHz, CDCl₃): δ 7.60 (m, 4H), 3.93 (s, 3H).

18 Ethyl-2-fluoro-4-hydroxy benzoate (Reagent I)

19 A solution of 2-fluoro-4-hydroxy benzoic acid (Intermediate 4, 3g,
20 19.2mmol) in ethanol (65mL) and benzene (90mL) was treated with
21 concentrated sulfuric acid (1.5mL) and heated at reflux overnight using a
22 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the
23 residue was diluted with water and diethyl ether. The phases were separated
24 and the organic phase was washed with saturated aqueous sodium
25 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous
26 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title
27 compound as a solid (3.07g, 86%).

1 ¹H-NMR (300 MHz, CD₃COCD₃): δ 1.34 (t, *J* = 7.1Hz, 3H), 4.32 (q, *J* =
2 7.1Hz, 2H), 6.66(dd, *J* = 2.6, 10.9Hz, 1H), 6.76 (dd, *J* = 2.3, 8.5Hz, 1H),
3 7.83(d, *J* = 8.4Hz, 1H), 9.91 (s, 1H).

4 Ethyl-2-fluoro-4-trifluoromethylsulfonyloxy-benzoate (Intermediate 6)

5 A stirred, cooled (ice bath) solution of ethyl-2-fluoro-4-hydroxy-
6 benzoate (**Intermediate 5**, 0.368g, 2mmol) and 2,6-di-*tert*-butyl-4-methyl-
7 pyridine (0.81g, 8mmol) in 8mL of dichloromethane was treated with
8 trifluoromethanesulfonic anhydride (0.1g, 4mmol). The reaction mixture
9 was allowed to warm to ambient temperature and stirred overnight. The
10 reaction mixture was subjected to flash column chromatography over silica
11 gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to
12 afford the title compound (0.53g, 85%).

13 ¹H-NMR (300 MHz, CDCl₃): δ 1.41 (t, *J* = 7.3Hz, 3H), 4.42 (q, *J* = 7.1Hz,
14 2H), 7.12-7.20(m, 2H), 8.08(t, *J* = 8.3Hz, 1H).

15 Ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate (Intermediate 7)

16 A solution of ethyl-2-fluoro-4- trifluoromethylsulfonyloxy-benzoate
17 (**Intermediate 6**, 1.82g, 6mmol) in triethyl amine (12mL) and anhydrous
18 tetrahydrofuran (30mL) was treated with copper(I)iodide (0.12g, 0.6mmol)
19 and sparged with argon. Dichlorobis(triphenylphosphine)palladium(II)
20 (0.43g, 0.6mmol) was added followed by (trimethylsilyl)acetylene (3.6mL,
21 24mmol) and the resulting reaction mixture was heated at 70°C overnight. It
22 was then cooled to ambient temperature, diluted with diethyl ether and
23 filtered over a bed of celite. The filtrate was evaporated in *vacuo* to an oil
24 which was subjected to flash column chromatography over silica gel (230-
25 400 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title
26 compound as an orange oil (1.5g, quantitative).

27 ¹H-NMR (300 MHz, CDCl₃):δ 0.011 (s, 9H), 1.13(t, *J* = 7.1Hz, 3H), 4.13 (q,

1 $J = 7.1\text{Hz}$, 2H), 6.93-7.02(m, 2H), 7.07 (s, 1H), 7.61(t, $J = 7.9\text{Hz}$, 1H).

2 Ethyl-4-ethynyl-2-fluoro benzoate (Reagent D)

3 A solution of ethyl-2-fluoro-4-trimethylsilanylethynyl-benzoate
4 (Intermediate 7, 1.5g, 6mmol) in ethanol (16mL) was treated with
5 potassium carbonate (1.485g, 10.74mmol) and stirred overnight at room
6 temperature. The reaction mixture was then diluted with water and extracted
7 with diethyl ether (x2). The combined organic phase was dried over
8 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford an
9 orange oil. Flash column chromatography over silica gel (230-400 mesh)
10 using 5% ethyl acetate in hexane as the eluent afforded the title compound
11 (1g, 86%).

12 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.39 (t, $J = 7.1\text{Hz}$, 3H), 3.26 (s, 1H), 4.39 (q,
13 $J = 7.1\text{Hz}$, 2H), 7.22-7.33 (m, 2H), 7.88(t, $J = 7.7\text{Hz}$, 1H).

14 Methyl-4-iodo-phenyl acetate (Reagent B)

15 A solution of 4-iodo phenyl acetic acid (5g, 19mmol) in methanol was
16 treated with concentrated sulfuric acid (0.5mL) and refluxed overnight. The
17 volatiles were distilled off in *vacuo* and the residue was dissolved in ethyl
18 acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and
19 evaporated in *vacuo* to an oil which was subjected to flash column
20 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in
21 hexane as the eluent to afford the title compound as a clear oil (5g, 95%).

22 $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.63 (d, 2H, $J = 8.5\text{Hz}$), 7.01 (d, 2H, $J =$
23 8.0Hz), 3.67 (s, 3H), 3.55 (s, 2H).

24 2-Fluoro-4-iodo-phenyl acetonitrile (Intermediate 2)

25 A solution of 2-fluoro-4-iodo-benzyl bromide (Intermediate 1,
26 2.56g, 8.15mmol) in ethanol (55mL and water (10mL) was treated with
27 sodium cyanide (2.15g, 43.86mmol) and refluxed for 0.5h. The volatiles

1 were distilled off in *vacuo* and the residue was diluted with water and
2 extracted with diethyl ether (x2). The combined organic extract was washed
3 with water (x1) and brine (x1), dried over anhydrous magnesium sulfate,
4 filtered and evaporated in *vacuo* to afford the title compound as a pale
5 yellow solid (2.05g, 96%).

6 ¹H-NMR (300 MHz, CDCl₃): δ 3.71(s, 3H), 7.16(t, *J* = 8.2Hz, 1H), 7.45(dd,
7 *J* = 1.7, 9.1Hz, 1H), 7.51(dd, *J* = 1.5, 8.2Hz, 1H).

8 2-Fluoro-4-iodo-phenyl acetic acid (**Intermediate 3**)

9 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,
10 2.05g, 7.83mmol) in ethanol (50mL) and water (15mL) was treated with
11 potassium hydroxide (3.4g, 60.7mmol) and refluxed for 4h. The volatiles
12 were distilled off in *vacuo* and the residue was diluted with water and poured
13 into cold, dilute hydrochloric acid and the precipitated solid was filtered.
14 The solid was dissolved in diethyl ether, and the organic solution was dried
15 over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to
16 afford the title compound a pale yellow solid (1.75g, 79%).

17 ¹H-NMR (300 MHz, CDCl₃): δ 3.64 (s, 2H), 6.98(t, *J* = 7.9Hz, 1H), 7.25-
18 7.46 (m, 2H), 9.60-10.40(br s, 1H).

19 Ethyl-2-fluoro-4-iodo-phenyl acetate (**Reagent C**)

20 A solution of 2-fluoro-iodo-phenyl acetic acid (**Intermediate 3**,
21 1.75g, 6.22mmol) in ethanol (50mL) and benzene (100mL) was treated with
22 concentrated sulfuric acid (1.4mL) and heated at reflux overnight using a
23 Dean-Stark water trap. The volatiles were distilled off in *vacuo* and the
24 residue was diluted with water and diethyl ether. The phases were separated
25 and the organic phase was washed with saturated aqueous sodium
26 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous
27 magnesium sulfate, filtered and evaporated in *vacuo* to afford an oil which

1 was subjected to flash column chromatography over silica gel (230-400
2 mesh) using 5%-10% ethyl acetate in hexane as the eluent to afford the title
3 compound as a pale yellow solid (1.4g, 73%).
4 ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, *J* = 7.1Hz, 3H), 3.60 (s, 2H), 4.16 (q,
5 *J* = 7.1Hz, 2H), 6.99(t, *J* = 8.0Hz, 1H), 7.39-7.44(m, 2H).

6 Methyl-2-fluoro-4-iodo-phenyl acetate (Reagent H)

7 A solution of 2-fluoro-4-iodo-phenyl acetonitrile (**Intermediate 2**,
8 3g, 11.45mmol) in methanol (50mL) and benzene (50mL) was treated with
9 *p*-toluene sulfonic acid (2.5g, 13.15mmol) and heated at reflux overnight
10 using a Dean-Stark water trap. The volatiles were distilled off in *vacuo* and
11 the residue was diluted with water and diethyl ether. The phases were
12 separated and the organic phase was washed with saturated aqueous sodium
13 bicarbonate (x1), water (x1) and brine (x1), dried over anhydrous
14 magnesium sulfate, filtered and evaporated in *vacuo* to afford an oil which
15 was subjected to flash column chromatography over silica gel (230-400
16 mesh) using 6% ethyl acetate in hexane as the eluent to afford the title
17 compound as a colorless oil (2.7g, 80%).
18 ¹H-NMR (300 MHz, CDCl₃): δ 3.62 (s, 2H), 3.70 (s, 3H), 6.99(t, *J* = 7.9Hz,
19 1H), 7.39-7.45(m, 2H).

20 GENERAL PROCEDURE A: 7-Methoxy-1,1-dimethyl-1,2,3,4-
21 tetrahydronaphthalene (Intermediate 8)

22 A stirred, cooled (-40°C) solution of titanium tetrachloride in
23 anhydrous dichloromethane (1M, 20mL) under argon, was treated with a
24 solution of dimethyl zinc (2M, 40mL) in toluene. After 0.5h, a solution of 7-
25 methoxy-1-tetralone (1.76g, 10mmol) in anhydrous dichloromethane (5mL)
26 was cannulated into the reaction mixture and the resulting solution was
27 allowed to warm to ambient temperature and stirred overnight. The reaction

1 mixture was then cooled to -40°C and cautiously quenched with methanol
2 (11mL). It was diluted with dichloromethane and saturated aqueous
3 ammonium chloride solution. The phases were separated and the aqueous
4 phase was extracted with dichloromethane (x2mL). The combined organic
5 phase was dried over anhydrous sodium sulfate, filtered and evaporated in
6 *vacuo* to the title compound (1.75g, 92%) as an oil.
7 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.33(s, 6H), 1.67-1.71(m, 2H), 1.79-1.90(m,
8 2H), 2.75(t, $J = 6.2\text{Hz}$, 2H), 3.83(s, 3H), 6.72(dd, $J = 2.6, 8.3\text{Hz}$, 1H),
9 6.93(d, $J = 2.6\text{Hz}$, 1H), 7.02(d, $J = 8.3\text{Hz}$, 1H).

10 GENERAL PROCEDURE B: 6-Methoxy-4,4-dimethyl-1,2,3,4-
11 tetrahydronaphthalene-1-one (Intermediate 9)

12 A solution of 7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene
13 (Intermediate 8, 1.65g, 8.7 mmol) in 7.5mL of glacial acetic acid was
14 cooled to 0°C and treated with a solution of chromium trioxide (2g, 20mmol)
15 in 8mL of acetic acid and 7mL of water. The reaction mixture was then
16 allowed to warm to ambient temperature and stirred overnight. It was
17 diluted with water and extracted with diethyl ether (x2). The combined
18 organic phase was washed with water (x1), saturated aqueous sodium
19 bicarbonate (x1) and brine (x1), dried over anhydrous magnesium sulfate,
20 filtered and evaporated in *vacuo* to afford the title compound (1.64g, 93%) as
21 a yellow oil.

22 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.34(s, 6H), 1.96(t, $J = 7.1\text{Hz}$, 2H), 2.64(t, J
23 $= 7.1\text{Hz}$, 2H), 3.83(s, 3H), 6.77(dd, $J = 2.6, 8.7\text{Hz}$, 1H), 6.83(d, $J = 2.5\text{Hz}$,
24 1H), 7.98(d, $J = 8.7\text{Hz}$, 1H).

25 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-one
26 (Intermediate 10)

1 A stirred, cooled (-78°C) solution of 6-methoxy-4,4-dimethyl-1,2,3,4-
2 tetrahydronaphthalene-1-one (**Intermediate 9**, 0.8, 3mmol) under argon was
3 treated with a 1M solution of boron tribromide (10mL). The reaction
4 mixture was allowed to warm to ambient temperature and stirred overnight.
5 The reaction mixture was cooled to -78°C, quenched and diluted with
6 saturated aqueous sodium bicarbonate solution and the aqueous phase was
7 extracted with dichloromethane (x2). The combined organic phase was
8 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an
9 oil. Flash column chromatography over silica gel (230-400 mesh) using
10 30% ethyl acetate in hexane as the eluent afforded the title compound (0.3g,
11 52%) as a yellow viscous oil.

12 ¹H-NMR (300 MHz, CDCl₃): δ 1.33(s, 6H), 1.97(t, *J* = 6.8Hz, 2H), 2.71(t, *J*
13 = 6.7Hz, 2H), 6.81(dd, *J* = 2.3, 8.5Hz, 1H), 6.94(d, *J* = 2.3Hz, 1H), 7.98(d,
14 *J* = 8.7Hz, 1H), 9.35(s, 1H).

15 GENERAL PROCEDURE C: 4,4-Dimethyl-6-trifluoromethylsulfonyloxy-
16 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 11**)

17 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-
18 tetrahydronaphthalene-1-one (**Intermediate 10**, 0.3g, 1.6mmol) in anhydrous
19 dichloromethane (10mL) was treated with 4-(dimethylamino)pyridine
20 (0.36g, 3.27mmol) followed by 2-[N,N'-bis(trifluoromethylsulfonyl)amino]-
21 5-chloropyridine (0.79g, 2mmol). After stirring at ambient temperature for
22 0.75h, the reaction mixture was diluted with dichloromethane and washed
23 with water (x1). The organic phase was dried over anhydrous sodium
24 sulfate, filtered and evaporated in *vacuo* to an oil. Flash column
25 chromatography over silica gel (230-400 mesh) using 8-10% ethyl acetate in
26 hexane as the eluent afforded the title compound (0.462g, 90%) as an off-
27 white solid.

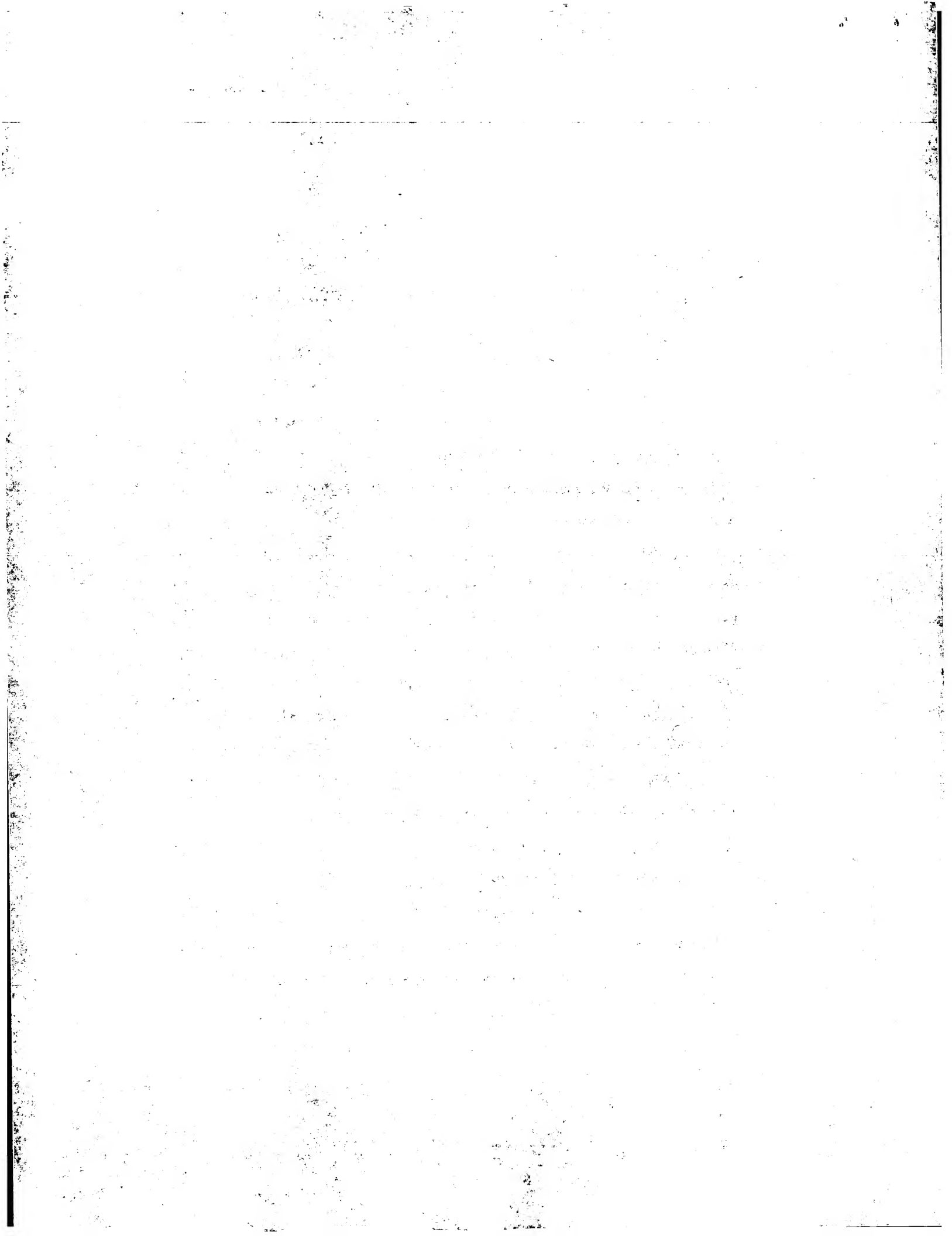
1 ¹H-NMR (300 MHz, CDCl₃): δ 1.36(s, 6H), 2.01(t, *J* = 6.8Hz, 2H), 2.70(t, *J*
2 = 6.7Hz, 2H), 7.15(dd, *J* = 2.5, 8.7Hz, 1H), 7.28(d, *J* = 2.4Hz, 1H), 8.06(d,
3 *J* = 8.7Hz, 1H).

4 GENERAL PROCEDURE D: 4,4-Dimethyl-6-trimethylsilyl-ethynyl-
5 1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 12**)

6 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
7 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.46g, 1.43mmol) in triethyl
8 amine (3mL) and anhydrous tetrahydrofuran (8mL) was treated with
9 copper(I)iodide (0.1g, 0.53mmol) and sparged with argon for 5 minutes.
10 Trimethylsilyl acetylene (0.85mL, 6mmol) was then added followed by
11 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol). The
12 resulting reaction mixture was heated at 70°C for 17h. It was then cooled to
13 ambient temperature, diluted with diethyl ether and filtered over a bed of
14 celite. The filtrate was evaporated *vacuo* to an oil which was subjected to
15 flash column chromatography over silica gel (230-400 mesh) using 5% ethyl
16 acetate in hexane as the eluent to afford the title compound (0.28g, 72%).
17 ¹H-NMR (300 MHz, CDCl₃): δ 0.26(s, 9H), 1.36(s, 6H), 1.99(t, *J* = 6.8Hz,
18 2H), 2.69(t, *J* = 6.7Hz, 2H), 7.35(dd, *J* = 1.7, 8.2Hz, 1H), 7.49 (unresolved
19 d, 1H), 7.93(d, *J* = 8.1Hz, 1H).

20 GENERAL PROCEDURE E: 6-Ethynyl-4,4-dimethyl-1,2,3,4-
21 tetrahydronaphthalene-1-one (**Intermediate 13**)

22 A solution of 4,4-dimethyl-6-trimethylsilyl-ethynyl-1,2,3,4-
23 tetrahydronaphthalene-1-one (**Intermediate 12**, 0.28g, 1.03mmol) in
24 methanol (10mL) was treated with potassium carbonate (0.74g, 5.35mmol)
25 and stirred at ambient temperature for 4h. The volatiles were distilled off in
26 *vacuo* and the residue was diluted with water and extracted with diethyl ether
27 (x2). The combined organic extract was dried over anhydrous magnesium



1 sulfate, filtered and evaporated in *vacuo* to afford the title compound (0.19g,
2 89%) as an oil that solidified on standing.

3 ¹H-NMR (300 MHz, CDCl₃): δ 1.33(s, 6H), 1.96(t, *J* = 6.8Hz, 2H), 2.67(t, *J*
4 = 6.8Hz, 2H), 3.25(s, 1H), 7.33(dd, *J* = 1.5, 8.1Hz, 1H), 7.49 (d, *J* = 1.5Hz,
5 1H), 7.13(d, *J* = 8.1Hz, 1H).

6 GENERAL PROCEDURE F: 4-(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-
7 naphthalene-2-yl-ethynyl)-benzoic acid ethyl ester (Intermediate 14)

8 A solution of 6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-
9 1-one (**Intermediate 13**, 0.23g, 1.1mmol) and ethyl-4-iodo benzoate
10 (**Reagent A**, 0.36g, 1.3mmol) in triethyl amine (7mL) and anhydrous
11 tetrahydrofuran (3mL) was treated with copper(I)iodide (0.114g, 0.6mmol)
12 and sparged with argon for 5 minutes.
13 Dichlorobis(triphenylphosphine)palladium(II) (0.23g, 0.33mmol) was added
14 and the reaction mixture was stirred overnight at room temperature. It was
15 diluted with diethyl ether and filtered over a bed of celite. The filtrate was
16 evaporated in *vacuo* to a brown oil that was subjected to flash column
17 chromatography over silica gel (230-400 mesh) using 6-7% ethyl acetate in
18 hexane as the eluent to afford the title compound (0.29g, 72%) as a pale
19 brown solid.

20 ¹H-NMR (300 MHz, CDCl₃): δ 1.3(t, *J* = 7.1Hz, 3H), 1.37(s, 6H), 1.80 (t, *J*
21 = 6.8Hz, 2H), 2.69(t, *J* = 6.8Hz, 2H), 4.35(q, *J* = 7.1Hz, 2H), 7.40(dd, *J* =
22 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.6Hz, 1H), 7.57 (d, *J* = 8.3Hz, 2H), 7.96(d, *J*
23 = 8.2Hz, 1H), 7.99(d, *J* = 8.5Hz, 2H).

24 GENERAL PROCEDURE G 4-(5-Cyclopropylamino-8,8-dimethyl-5,6,7,8-
25 tetrahydro-naphthalene-2yl-ethynyl)-benzoic acid ethyl ester (Compound 1,
26 **General Formula 4)**

1 A solution of 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-
2 2-ylethynyl)-benzoic acid ethyl ester (**Intermediate 14**, 0.14g, 0.4mmol) in
3 3mL of dichloromethane and 2mL of acetonitrile was treated with
4 cyclopropyl amine(1mL, 14.45mmol). After 5 minutes, acetic acid (1mL)
5 was added followed by sodium cyanoborohydride (0.13g, 2mmol). The
6 reaction was stirred overnight at ambient temperature. It was then diluted
7 with water and saturated aqueous sodium carbonate solution and extracted
8 with dichloromethane (x2). The combined organic extract was dried over
9 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash
10 column chromatography over silica gel (230-400 mesh) using 20% ethyl
11 acetate in hexane as the eluent afforded the title compound (0.1g, 62%) as a
12 pale yellow solid.

13 ¹H-NMR (300 MHz, CDCl₃): δ 0.30-0.60(m, 4H), 1.28(s, 3H), 1.35 (s, 3H),
14 1.30(t, *J* = 7.1Hz, 3H), 1.55-1.61(m, 1H), 1.83-2.05(m, 3H), 2.25 (quintet, *J*
15 = 3.0 Hz, 1H), 3.80 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.27-7.36(m,
16 2H), 7.52 (s, 1H), 7.55(d, *J* = 8.3Hz, 2H), 8.03(d, *J* = 8.5Hz, 2H).

17 GENERAL PROCEDURE H 4-[(5-Cyclopropyl-methyl-amino)-8,8-
18 dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl
19 ester (**Compound 2**, General Formula 4)

20 A solution of 4-(5-cyclopropylamino-8,8-dimethyl-5,6,7,8-tetrahydro-
21 naphthalene-2-ylethynyl)-benzoic acid ethyl ester (**Compound 1**, 0.064g,
22 0.16mmol) in acetone (2mL) was treated with potassium carbonate (0.6g,
23 4.34mmol) and methyl iodide (1mL, 16mmol) and stirred overnight at
24 ambient temperature. The volatiles were distilled off in *vacuo* and the
25 residue was diluted with water and extracted with dichloromethane (x2).
26 The combined organic extract was dried over anhydrous sodium sulfate,
27 filtered and evaporated in *vacuo* to afford the title compound (0.065g, 99%).

¹H-NMR (300 MHz, CDCl₃): δ 0.28-0.49 (m, 4H), 1.21(s, 3H), 1.26 (s, 3H), 1.33 (t, *J* = 7.1Hz, 3H), 1.58-1.73 (m, 2H), 1.83-1.89 (m, 2H), 2.02-2.08 (m, 1H), 2.06 (s, 3H), 3.88 (t, *J* = 8.1Hz, 1H), 4.32(q, *J* = 7.1Hz, 2H), 7.20(d, *J* = 7.8Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.8Hz, 1H), 7.52(d, *J* = 8.4Hz, 2H), 8.03(d, *J* = 8.3Hz, 2H).

GENERAL PROCEDURE I: 4-[(5-Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid

(**Compound 3, General Formula 4**) A solution of 4-[(5-cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-benzoic acid ethyl ester (**Compound 2**, 0.065g, 0.158mmol) in ethanol (1mL) and tetrahydrofuran (1mL) was treated with 1M aqueous sodium hydroxide solution (1mL) and heated at 80°C for 1h. The volatiles were distilled off in *vacuo* and the residue was diluted with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (x2). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a solid that was washed with dichloromethane and dried to afford the title compound (0.029g, 38%) as a white solid.

¹H-NMR (300 MHz, CD₃COCD₃): δ 0.35-0.51(m, 4H), 1.26(s, 3H), 1.29 (s, 3H), 1.60-1.82(m, 2H), 1.88-2.02(m, 2H), 2.02-2.15 (m, 1H), 2.10 (s, 3H), 3.93 (t, *J* = 8.0Hz, 1H), 7.26(dd, *J* = 1.5, 8.2Hz, 1H), 7.51 (d, *J* = 1.5Hz, 1H), 7.52(d, *J* = 8.2Hz, 1H), 7.62(d, *J* = 8.5Hz, 2H), 8.02(d, *J* = 8.2Hz, 2H).
4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester (**Compound 4, General Formula 8**)

Following general procedure F and using 6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene-1-one (**Intermediate 13**, 0.312g, 1.5mmol), 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.50g, 1.8mmol), triethyl

1 amine (7mL), anhydrous tetrahydrofuran (3mL), copper(I)iodide (0.04g,
2 0.2mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.15g,
3 0.213mmol) followed by flash column chromatography over silica gel (230-
4 400 mesh) using 16-20% ethyl acetate in hexane as the eluent, the title
5 compound was obtained as a pale yellow solid (0.42g, 76%).
6 ¹H-NMR (300 MHz, CDCl₃): δ 1.42(s, 6H), 2.04(t, *J* = 6.7Hz, 2H), 2.74(t, *J*
7 = 6.7Hz, 2H), 3.66(s, 2H), 3.71(s, 3H), 7.29 (d, *J* = 8.2Hz, 2H), 7.43(dd, *J* =
8 1.5, 7.9Hz, 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.57 (d, *J* = 1.5Hz, 1H), 8.00(d, *J*
9 = 8.2Hz, 1H).
10 GENERAL PROCEDURE J: 4-[(8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-
11 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 5, General
12 Formula 8)
13 A solution of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-
14 2-ylethynyl)-phenyl]-acetic acid methyl ester (Compound 4, 0.1g,
15 0.28mmol) in a mixture of methanol (2mL), tetrahydrofuran (3.5mL) and
16 water (1.5mL) was treated with lithium hydroxide monohydrate (0.11g,
17 2.62mmol) and the resulting reaction mixture was stirred at ambient
18 temperature for 3h. The volatiles were distilled off in *vacuo* and the residue
19 was diluted with water and dilute hydrochloric acid and extracted with ethyl
20 acetate (x3). The combined organic phase was dried over anhydrous sodium
21 sulfate, filtered and evaporated in *vacuo* to afford the title compound as a
22 pale yellow solid (0.088g, 92%).
23 ¹H-NMR (300 MHz, CDCl₃): δ 1.41(s, 6H), 2.02(t, *J* = 6.7Hz, 2H), 2.74(t, *J*
24 = 6.8Hz, 2H), 3.68(s, 2H), 7.28 (d, *J* = 8.2Hz, 2H), 7.42(dd, *J* = 1.5, 8.2Hz,
25 1H), 7.52 (d, *J* = 8.2Hz, 2H), 7.56 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 8.2Hz,
26 1H).

1 4-[(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-
2 yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 6, General
3 Formula 4)

4 Following general procedure G and using 4-[(8,8-dimethyl-5-oxo-
5 5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester
6 (**Compound 4**, 0.2g, 0.54mmol), dichloromethane (4mL), acetonitrile(2mL),
7 cyclopropyl amine(1mL, 14.45mmol), acetic acid (1mL)and sodium
8 cyanoborohydride (0.16g, 2.54mmol) followed by flash column
9 chromatography over silica gel (230-400 mesh) using 30% ethyl acetate in
10 hexane as the eluent the title compound was obtained as a pale yellow oil
11 (0.22g, 99%).

12 ¹H-NMR (300 MHz, CDCl₃): δ 0.38-0.60 (m, 4H), 1.26(s, 3H), 1.33(s, 3H),
13 1.50-1.59(m, 1H), 1.79-2.10 (m, 3H), 2.25(m, 1H), 3.63(s, 2H), 3.69(s, 3H),
14 3.79(t, *J* = 4.8Hz, 1H), 7.20-7.32 (m, 4H), 7.47(s, 1H), 7.58(d, *J* = 8.2Hz,
15 2H).

16 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
17 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid methyl ester (Compound 7,
18 General Formula 4)

19 Following general procedure H and using 4-[(5-(cyclopropyl-amino)-
20 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-phenyl]-acetic
21 acid methyl ester (**Compound 6**, 0.15g, 0.37mmol), acetone (5mL),
22 potassium carbonate (1.1g, 7.95mmol) and methyl iodide (1mL, 16mmol),
23 the following work-up was used. The volatiles were distilled off in *vacuo*
24 and the residue was diluted with water and extracted with dichloromethane
25 (x2). The combined organic extract was dried over anhydrous sodium
26 sulfate, filtered and evaporated in *vacuo* to afford the title compound
27 (0.148g, 97%).

1 ¹H-NMR (300 MHz, CDCl₃): δ 0.38-0.58(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),
2 1.68-1.81(m, 2H), 1.85-1.98(m, 2H), 2.08-2.15 (m, 1H), 2.12 (s, 3H), 3.62(s,
3 2H), 3.69(s, 3H), 3.94 (t, *J* = 7.9Hz, 1H), 7.24(d, *J* = 8.2Hz, 1H), 7.24 (d, *J*
4 = 8.2Hz, 2H), 7.44-7.51(m, 4H).

5 4-[(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
6 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid (Compound 8, General
7 Formula 4)

8 Following general procedure J and using 4-[(5-(cyclopropyl-methyl-
9 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-phenyl]-
10 acetic acid methyl ester (**Compound 7**, 0.148g, 0.357mmol), methanol
11 (2mL), tetrahydrofuran (4mL), water (1mL) and lithium hydroxide
12 monohydrate (0.25g, 5.95mmol) followed by flash column chromatography
13 over silica gel (230-400 mesh) using 30-75% ethyl acetate in hexane as the
14 eluent, the title compound was obtained as a white solid (0.08g, 56%).
15 ¹H-NMR (300 MHz, CDCl₃): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,
16 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),
17 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.24(dd, *J* = 1.5, 8.2Hz,
18 1H), 7.26 (d, *J* = 8.2Hz, 2H), 7.43 (d, *J* = 8.2Hz, 1H), 7.47(s, 1H), 7.47(d, *J*
19 = 8.2Hz, 2H), 10.37(br s, 1H).

20 2-Fluoro-4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-
21 ethynyl)]benzoic acid ethyl ester (Compound 9, General Formula 8)

22 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
23 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.3g, 0.9mmol),
24 copper(I)iodide (0.057g, 0.3mmol) and ethyl-2-fluoro-4-ethynyl-benzoate
25 (**Reagent D**, 0.44g, 2.27mmol) in triethyl amine (2mL) and tetrahydrofuran
26 (3mL) was sparged with argon for 5 minutes and treated with
27 dichlorobis(triphenylphosphine)palladium(II) (0.135g, 0.192mmol) and

1 stirred at room temperature overnight and then refluxed for 2h. It was then
2 cooled to ambient temperature, diluted with diethyl ether and filtered over a
3 bed of celite. The filtrate was evaporated in *vacuo* to an oil which was
4 subjected to flash column chromatography over silica gel (230-400 mesh)
5 using 10-15% ethyl acetate in hexane as the eluent to afford the title
6 compound as a yellow solid (0.22g, 67%).

7 ¹H-NMR (300 MHz, CDCl₃): δ 1.38 (t, *J* = 7.0Hz, 3H), 1.39(s, 6H), 2.01(t, *J*
8 = 6.7Hz, 2H), 2.71(t, *J* = 6.7Hz, 2H), 4.37(q, *J* = 7Hz, 2H), 7.28(dd, *J* = 0.9,
9 10Hz, 1H), 7.34(dd, *J* = 0.9, 8.2Hz, 1H), 7.41 (dd, *J* = 1.5, 8.2Hz, 1H),
10 7.57(d, *J* = 0.9Hz), 7.90(t, *J* = 7.9Hz, 1H), 7.93 (d, *J* = 7.9Hz, 1H).

11 2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
12 benzoic acid (Compound 10, General Formula 8)

13 A solution of 2-fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-
14 naphthalen-2-ylethynyl)benzoic acid ethyl ester (Compound 9, 0.1g,
15 0.274mmol) in ethanol(4mL), methanol (2mL) and tetrahydrofuran (2mL)
16 was treated with 1M aqueous sodium hydroxide solution and heated at 70°C
17 for 1h. The volatiles were distilled off in *vacuo* and the residue was diluted
18 with water and dilute hydrochloric acid and extracted with ethyl acetate (x2).
19 The combined organic extract was dried over anhydrous sodium sulfate,
20 filtered and evaporated in *vacuo* to afford a solid that was recrystallized from
21 hot aqueous acetonitrile to afford the title compound (0.025g, 27%).

22 ¹H-NMR (300 MHz, CDCl₃): δ 1.43(s, 6H), 2.05(t, *J* = 6.9Hz, 2H), 2.76(t, *J*
23 = 6.9Hz, 2H), 7.26-7.47(m, 3H), 7.60(d, *J* = 1.1Hz, 1H), 7.99-8.05(m, 2H).

24 4-[5-(Cyclopropyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-
25 yl-ethynyl]-2-fluoro-benzoic acid ethyl ester (Compound 11, General
26 Formula 4)

27 Following general procedure G and using 2-fluoro-4-(8,8-dimethyl-5-
28 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-benzoic acid ethyl ester

1 (Compound 9, 0.132g, 0.3mmol), dichloromethane (4mL),
2 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid
3 (1mL)and sodium cyanoborohydride (0.18g, 2.86mmol) followed by flash
4 column chromatography over silica gel (230-400 mesh) using 16-20% ethyl
5 acetate in hexane as the eluent, the title compound was obtained as a pale
6 yellow oil (0.1g, 82%).

7 ¹H-NMR (300 MHz, CDCl₃):δ 0.36-0.54 (m, 4H), 1.27(s, 3H), 1.33(s, 3H),
8 1.40(t, *J* = 7.0Hz, 3H), 1.54-1.61(m, 2H), 1.82-2.05 (m, 2H), 2.26(m, 1H),
9 3.79 (t, *J* = 4.9Hz, 1H), 4.39(q, *J* = 7.1Hz, 2H), 7.26-7.50(m, 4H), 7.87(s,
10 1H), 7.92 (t, *J* = 7.9Hz, 1H).

11 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
12 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid ethyl ester (Compound 12,

13 **General Formula 4)**

14 Following general procedure H and using 4-[5-(cyclopropyl-methyl-
15 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-
16 benzoic acid ethyl ester (Compound 11, 0.1g, 0.246mmol), acetone (4mL),
17 potassium carbonate (0.917g, 6.63mmol) and methyl iodide (0.8mL,
18 11mmol), the following work-up was used. The volatiles were distilled off
19 in *vacuo* and the residue was diluted with water and extracted with
20 dichloromethane (x2). The combined organic extract was dried over
21 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an oil. Flash
22 column chromatography over silica gel (230-400 mesh) using 8-10% ethyl
23 acetate in hexane as the eluent afforded the title compound as a pale yellow
24 oil (0.102g, 98%).

25 ¹H-NMR (300 MHz, CDCl₃): δ 0.39-0.62 (m, 4H), 1.29(s, 3H), 1.34(s, 3H),
26 1.42(t, *J* = 6.9Hz, 3H), 1.65-1.82(m, 2H), 1.85-2.02 (m, 2H), 2.02-2.10(m,

1 1H), 2.15(s, 3H), 3.97(t, $J = 7.7\text{Hz}$, 1H), 4.42(q, $J = 7.0\text{Hz}$, 2H), 7.28-7.36
2 (m, 3H), 7.59(s, 1H), 7.55(d, $J = 7.9\text{Hz}$, 2H), 7.92 (t, $J = 7.5\text{Hz}$, 1H).
3 4-[5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
4 naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid (Compound 13, General
5 Formula 4)

6 Following general procedure I and using 4-[(5-cyclopropyl-methyl-
7 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl]-2-fluoro-
8 benzoic acid ethyl ester (Compound 12, 0.102g, 0.23mmol), ethanol (4mL)
9 and 1M aqueous sodium hydroxide solution (2mL) followed by flash
10 column chromatography over silica gel (230-400 mesh) 30% ethyl acetate in
11 hexane as the eluent, the title compound was obtained as an off-white
12 solid(0.015g, 16%).

13 $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.54-0.65 (m, 4H), 1.29 (s, 3H), 1.32 (s, 3H),
14 1.68-1.83 (m, 2H), 1.97-2.05 (m, 2H), 2.18-2.25 (m, 1H), 2.25 (s, 3H), 4.13
15 (t, $J = 6.7\text{Hz}$, 1H), 7.26-7.30 (m, 2H), 7.34 (dd, $J = 1.5, 7.9\text{Hz}$, 1H), 7.48 (d,
16 $J = 1.8\text{Hz}$, 1H), 7.60 (d, $J = 8.5\text{Hz}$, 1H), 7.95 (t, $J = 7.9\text{Hz}$, 1H).
17 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-
18 ethynyl)-phenyl]acetic acid ethyl ester (Compound 14, General Formula
19 8)

20 Following general procedure F and using 6-ethynyl-4,4-dimethyl-
21 1,2,3,4-tetrahydro-naphthalene-1-one (Intermediate 13, 0.298g, 1.43mmol),
22 2-fluoro-4-iodo phenyl acetic acid ethyl ester (Reagent C, 0.44g,
23 1.43mmol), triethyl amine (Intermediate 13, 3mL), anhydrous
24 tetrahydrofuran (7mL), copper(I)iodide (0.04g, 0.2mmol) and
25 dichlorobis(triphenylphosphine)palladium(II) (0.15g, 0.213mmol) followed
26 by flash column chromatography over silica gel (230-400 mesh) using 14-

1 16% ethyl acetate in hexane as the eluent, the title compound was obtained
2 as an oil (0.43g, 77%).

3 ¹H-NMR (300 MHz, CDCl₃): δ 1.26(t, *J* = 7.2Hz, 3H), 1.41(s, 6H), 2.04(t, *J*
4 = 6.7Hz, 2H), 2.74(t, *J* = 6.7Hz, 2H), 3.68(s, 2H), 4.18(q, *J* = 7.1Hz, 2H),
5 7.23-7.57(m, 4H), 7.59 (d, *J* = 1.5Hz, 1H), 7.99(d, *J* = 7.9Hz, 1H).

6 [2-Fluoro-4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-
7 ethynyl)phenyl]-acetic acid (Compound 15, General Formula 8)

8 Following general procedure J and using [2-fluoro-4-(8,8-dimethyl-5-
9 oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)phenyl]acetic acid methyl
10 ester (**Compound 14**, 0.18g, 0.48mmol), methanol (4mL), tetrahydrofuran
11 (8mL), water (2mL) and lithium hydroxide monohydrate (0.2g, 4.76mmol)
12 followed by flash column chromatography over silica gel (230-400 mesh)
13 using 50- 100% ethyl acetate in hexane as the eluent, the title compound was
14 obtained as a dirty white solid (0.068g, 41%).

15 ¹H-NMR (300 MHz, CDCl₃): δ 1.41(s, 6H), 2.03(t, *J* = 6.7Hz, 2H), 2.74(t, *J*
16 = 6.8Hz, 2H), 3.73(s, 2H), 7.24-7.32(m, 3H), 7.42(dd, *J* = 1.5, 7.9Hz, 1H),
17 7.56 (s, 1H), 7.99(d, *J* = 7.9Hz, 1H), 9.40-10.00 (br s, 1H).

18 [4-(5-(Cyclopropyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-
19 yl-ethynyl)-2-fluoro-phenyl] acetic acid ethyl ester (Compound 16,
20 **General Formula 4)**

21 Following general procedure G and using [2-fluoro-4-(8,8-dimethyl-
22 5-oxo-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl) phenyl]acetic acid ethyl
23 ester (**Compound 14**, 0.258g, 0.68mmol), dichloromethane (4mL),
24 acetonitrile(2mL), cyclopropyl amine(1mL, 14.45mmol), acetic acid
25 (1mL)and sodium cyanoborohydride (0.266g, 4.23mmol) followed by flash
26 column chromatography over silica gel (230-400 mesh) using 16-20-25%

1 ethyl acetate in hexane as the eluent, the title compound was obtained as a
2 pale yellow oil (0.21g, 73%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 0.35-0.54 (m, 4H), 1.25(t, *J* = 7.1Hz, 3H),
4 1.26(s, 3H), 1.32(s, 3H), 1.53-1.64(m, 1H), 1.82-2.05 (m, 3H), 2.21-2.28(m,
5 1H), 3.65(s, 2H), 3.78(t, *J* = 5.0Hz, 1H), 4.17(q, *J* = 7.1Hz, 2H), 7.19-7.41
6 (m, 5H), 7.47(d, *J* = 1.5Hz, 1H).

7 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
8 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid ethyl ester
9 **(Compound 17, General Formula 8)**

10 Following general procedure H and using [4-((5-cyclopropyl-amino)-
11 8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2ylethynyl)-2-fluoro-
12 phenyl]acetic acid ethyl ester (**Compound 16**, 0.21g, 0.5mmol), acetone
13 (5mL), potassium carbonate (1.13g, 8.17mmol) and methyl iodide (0.5mL,
14 8mmol), the following work-up was used. The volatiles were distilled off in
15 *vacuo* and the residue was diluted with water and extracted with
16 dichloromethane (x2). The combined organic extract was dried over
17 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford an oil.
18 Flash column chromatography over silica gel (230-400 mesh) using 8% ethyl
19 acetate in hexane as the eluent afforded the title compound (0.15g, 69%).
20 ¹H-NMR (300 MHz, CDCl₃): δ 0.39-0.53(m, 4H), 1.27(s, 3H), 1.31 (s, 3H),
21 1.66-1.81(m, 2H), 1.89-2.05(m, 2H), 2.08-2.13 (m, 1H), 2.13 (s, 3H), 3.62(s,
22 2H), 3.94 (t, *J* = 8.0Hz, 1H), 4.16(q, *J* = 7.1Hz, 2H), 7.20-7.29(m, 4H),
23 7.44(d, *J* = 1.5Hz, 1H), 7.51 (d, *J* = 8.2Hz, 1H).

24 [4-(5-(Cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-
25 naphthalene-2-yl-ethynyl)-2-fluoro-phenyl]-acetic acid (**Compound 18,**
26 **General Formula 4)**

27 Following general procedure J and using [4-(5-(cyclopropyl-methyl-
28 amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)-2-fluoro-

1 phenyl]-acetic acid ethyl ester (**Compound 17**, 0.025g, 0.059mmol),
2 methanol (1mL), tetrahydrofuran (1mL), water (0.5mL) and lithium
3 hydroxide monohydrate (0.060g, 1.43mmol), the title compound was
4 obtained as a white solid (0.023g, 95%).
5 ¹H-NMR (300 MHz, CDCl₃): δ 0.52-0.54(m, 2H), 0.68-0.70(m, 2H), 1.27(s,
6 3H), 1.29(s, 3H), 1.63-1.80(m, 2H), 1.95-2.17(m, 2H), 2.19-2.24(m, 1H),
7 2.24(s, 3H), 3.60(s, 2H), 4.18(t, *J* = 7.7Hz, 1H), 7.19-7.28(m, 4H), 7.45 (d, *J*
8 = 1.5Hz, 1H), 7.49(d, *J* = 8.2Hz, 1H), 8.80-9.20(br s, 1H).

9 GENERAL PROCEDURE K: 8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalene-
10 1-one-2-carboxylic acid-4-(tert-butoxycarbonylmethyl)phenyl ester
11 **Compound 19, General Formula 8)**

12 A solution of 4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
13 tetrahydronaphthalene-1-one (**Intermediate 11**, 0.14g, 0.434mmol), *t*-butyl-
14 4-hydroxy-phenyl acetate (**Reagent E**, 0.14g, 0.673mmol), palladium acetate
15 (0.054g, 0.24mmol) and 1,3-bis(diphenylphosphino)propane (0.082g,
16 0.2mmol) in a mixture of dimethylsulfoxide (1mL), 1,2-dichloroethane
17 (1.5mL) and triethyl amine (1mL) was heated at 70°C under an atmosphere
18 of carbon monoxide overnight. The volatiles were distilled off in *vacuo* and
19 the residue was diluted with water and extracted with diethyl ether (x3). The
20 combined organic extract was dried over anhydrous magnesium sulfate,
21 filtered and evaporated in *vacuo* to an oil which was subjected to flash
22 column chromatography over silica gel (230-400 mesh) using 15% ethyl
23 acetate in hexane as the eluent to afford the title compound (0.11g, 53%).
24 ¹H-NMR (300 MHz, CDCl₃): δ 1.44(s, 3H), 1.44(s, 9H), 1.46 (s, 3H), 2.07(t,
25 *J* = 6.9Hz, 2H), 2.76(t, *J* = 6.8Hz, 2H), 3.55(s, 2H), 7.17 (d, *J* = 8.5Hz, 2H),
26 7.35(d, *J* = 8.5Hz, 2H), 8.05-8.13(m, 2H), 8.25 (d, *J* = 1.5Hz, 1H).

1 8,8-Dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-
2 (carboxymethyl)phenyl ester (Compound 20, General Formula 8)

3 A solution of 8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-
4 carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (Compound 19,
5 0.11g, 0.229mmol) in dichloromethane (2mL) was treated with
6 trifluoroacetic acid (0.85mL and stirred at ambient temperature for 2.5h.
7 The volatiles were distilled off in *vacuo* and the residue was diluted with
8 water and extracted with ethyl acetate (x3). The combined organic phase
9 was dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to
10 afford a solid which was subjected to flash column chromatography over
11 silica gel (230-400 mesh) using ethyl acetate as the eluent to afford the title
12 compound (0.024g, 25%).

13 ¹H-NMR (300 MHz, CDCl₃): δ 1.46 (s, 6H), 2.08(t, *J* = 6.7Hz, 2H), 2.80(t, *J*
14 = 6.7Hz, 2H), 3.70(s, 2H), 7.20(d, *J* = 8.5Hz, 2H), 7.37(d, *J* = 8.5Hz, 2H),
15 8.08(dd, *J* = 1.4, 8.2Hz, 1H), 8.14 (d, *J* = 8.2Hz, 1H), 8.24 (d, *J* = 1.2Hz,
16 1H). 5-Methoxy-3,3-dimethyl-indane (Intermediate 15)

17 Following general procedure A and using titanium tetrachloride
18 (5.5mL, 50mmol), anhydrous dichloromethane (80mL), 2M solution
19 dimethyl zinc (50mL) in toluene and a solution of 6-methoxy-indane-1-one
20 (4.05g, 25mmol) in dichloromethane (10mL) the title compound was
21 obtained as an oil (3.13g, 71%).

22 ¹H-NMR (300 MHz, CDCl₃): δ 1.37 (s, 6H), 2.04(t, *J* = 7.2Hz, 2H), 2.94(t, *J*
23 = 7.2Hz, 2H), 3.89(s, 3H), 6.82(d, *J* = 2.1Hz, 1H), 7.28(dd, *J* = 2.1, 7.0Hz,
24 1H), 7.35 (d, *J* = 7.0Hz, 1H).

25 5-Methoxy-3,3-dimethyl-indane-1-one (Intermediate 16)

26 Following general procedure B and using 5-methoxy-3,3-dimethyl
27 indane (Intermediate 15, 3.13g, 17.78mmol) in 20mL of glacial acetic acid

1 and a solution of chromium trioxide (3.91g, 39.1mmol) in 20mL of acetic
2 acid and 20mL of water the title compound was obtained as a viscous yellow
3 oil (3.3g, 97%).

4 ¹H-NMR (300 MHz, CDCl₃): δ 1.37 (s, 6H), 2.54 (s, 2H), 3.87(s, 3H), 6.86-
5 6.87 (m, 2H), 7.60 (d, *J* = 7.0Hz, 1H).

6 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-1-one
7 **(Intermediate 17)**

8 A solution of 5-methoxy-3,3-dimethyl-indane-1-one (**Intermediate**
9 **16**, 3.3g, 17.4mmol) in benzene (50mL) was treated with concentrated
10 sulfuric acid (10mL) and heated to 60°C. Sodium azide (1.95g, 30mmol)
11 was added in small portions and after the addition was complete, the reaction
12 mixture was heated further for 4h. It was then cooled, diluted with water and
13 extracted with chloroform (x3). The combined organic phase was dried over
14 anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to afford the
15 title compound as a brown solid (3.5g, quantitative by weight).

16 ¹H-NMR (300 MHz, CDCl₃): δ 1.31 (s, 6H), 3.28 (s, 2H), 3.83(s, 3H), 6.78
17 (d, *J* = 2.6Hz, 1H), 6.82(dd, *J* = 2.6Hz, 8.5Hz, 1H), 7.59 (s, 1H), 8.02 (d, *J* =
18 8.2Hz, 1H).

19 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 18**)

20 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-
21 isoquinoline-1-one (**Intermediate 17**, 3.5g, 17mmol) in 100mL of
22 anhydrous tetrahydrofuran was treated with lithium aluminum hydride (1.3g,
23 34.25mmol) in small portions and the resulting suspension was refluxed for
24 3 hours under argon. The reaction mixture was then cooled in an ice bath
25 and cautiously quenched with saturated aqueous sodium sulfate solution and
26 the resulting slurry was filtered and the filter-cake washed well with ethyl
27 acetate. The filtrate and washings were evaporated in *vacuo* to a brown oil

1 which was dissolved in chloroform, the solution was dried over anhydrous
2 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title
3 compound (3.2g, ~100%).
4 ¹H-NMR (300 MHz, CDCl₃): δ 1.27 (s, 6H), 2.22 (s, 1H), 2.84 (s, 2H), 3.79
5 (s, 3H), 3.95 (s, 2H), 6.68(dd, *J* = 2.4Hz, 8.3Hz, 1H), 6.86(d, *J* = 2.4Hz, 1H),
6 6.91 (d, *J* = 8.3Hz, 1H).

7 6-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde
8 **(Intermediate 19)**

9 A solution of 6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline
10 **(Intermediate 18, 3.2g, 16.7mmol)** in anhydrous dichloromethane (40mL)
11 was treated with formic acid (1mL, 26.5mmol) followed 1-(3-
12 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.9g, 20.34mmol)
13 and the resulting solution was stirred at ambient temperature overnight. It
14 was then diluted with chloroform and washed with water (x1) and brine (x1),
15 dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to
16 afford the title compound as pale brown viscous oil (3.26g, 90%).
17 ¹H-NMR (300 MHz, CDCl₃): δ 1.28 (s, 6H), 3.32 (s, 0.7H), 3.54 (s, 0.3H),
18 3.79(s, 3H), 4.54 (s, 0.3H), 4.66(s, 0.7H), 6.71(dd, *J* = 2.6Hz, 8.2Hz, 1H),
19 6.85-6.97(m, 1H), 7.02-7.27(m, 1H), 8.15(s, 0.7H), 8.34(s, 0.3H), 8.40-8.80
20 (br s, 1H).

21 6-Hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde
22 **(Intermediate 20)** A stirred, cooled (-78°C) solution of 6-methoxy-4,4-
23 dimethyl-1,2,3,4-tetrahydro-isoquinoline-2-carbaldehyde (**Intermediate 19,**
24 3.26g, 15mmol) in anhydrous dichloromethane (15mL) was treated with 1M
25 solution of boron tribromide in dichloromethane (50mL) stirred at ambient
26 temperature for 3h. It was then cooled again to 78°C and quenched carefully
27 with saturated aqueous sodium carbonate solution, diluted with water and the
28 aqueous phase was extracted with ethyl acetate (x2). The combined organic

1 extract was dried over anhydrous sodium sulfate, filtered and evaporated in
2 *vacuo* to afford the title compound as a solid foam (3g, 99%).

3 ¹H-NMR (300 MHz, CDCl₃): δ 1.23 (s, 6H), 3.31 (s, 0.7H), 3.54 (s, 0.3H),
4 4.51 (s, 0.3H), 4.64 (s, 0.7H), 6.70-6.75(m, 1H), 6.84-6.90(m, 2H), 7.50-
5 7.80(br s, 1H), 8.12(s, 0.7H), 8.32(s, 0.3H).

6 2-Cyclopropyl-6-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline
7 **(Intermediate 21)**

8 A stirred, cooled (0°C) solution of 6-hydroxy-4,4-dimethyl-1,2,3,4-
9 tetrahydro-isoquinoline-2-carbaldehyde (**Intermediate 20**, 2.3g, 11.21mmol)
10 in anhydrous tetrahydrofuran (40mL) under argon was treated with titanium
11 tetra-*iso*-propoxide (8.28mL, 28mmol) followed by 3M solution of ethyl
12 magnesium bromide in diethyl ether (18.7mL) and the reaction mixture was
13 then heated at 55°C overnight. It was then cooled in an ice-bath, quenched
14 with saturated aqueous ammonium chloride solution and extracted with
15 diethyl ether (x2). The combined organic phase was dried over anhydrous
16 sodium sulfate, filtered and evaporated in *vacuo* to afford a yellow oily solid.
17 Flash column chromatography over silica gel (230-400 mesh) using 10-20%
18 ethyl acetate in hexane as the eluent afforded the title compound as a pale
19 yellow solid (1.55g, 63%).

20 ¹H-NMR (300 MHz, CD₃COCD₃): δ 0.016-0.16(m, 4H), 0.847 (s, 6H), 1.37
21 (m, 1H), 2.20(s, 2H), 3.25 (s, 2H), 6.22(dd, *J* = 2.4, 8.2Hz, 1H), 6.41(d, *J* =
22 2.6Hz, 1H), 6.47(d, *J* = 8.2Hz, 1H), 7.62(s, 1H).

23 2-Cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-
24 tetrahydro-isoquinoline (**Intermediate 22**)

25 Following general procedure C and using 2-cyclopropyl-6-hydroxy-
26 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline (**Intermediate 21**, 1.5g,
27 6.9mmol) in anhydrous dichloromethane (30mL), triethyl amine (1.5mL,
28 10.39mmol) and [N,N'-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine

(2.75g, 7mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 8% ethyl acetate in hexane as the eluent the title compound was obtained (2.23g, 92%) as oil. ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.54(m, 4H), 1.25(s, 6H), 1.76(m, 1H), 2.62(s, 2H), 3.74(s, 2H), 6.98(dd, *J* = 2.3, 8.4Hz, 1H), 7.16(d, *J* = 8.2Hz, 1H), 7.14(d, *J* = 2.3Hz, 1H).

Ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (Intermediate 23)

Following general procedure K and using 2-cyclopropyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydro-isoquinoline (Intermediate 22, 1.6g, 4.6mmol), palladium acetate (0.127g, 0.56mmol), 1,3-bis(diphenylphosphino)propane (0.160g, 0.39mmol), dimethylsulfoxide (2mL), 1,2-dichloroethane (5mL), triethyl amine (2mL), ethanol (5mL) and an atmosphere of carbon monoxide followed by flash column chromatography over silica gel (230-400 mesh) using 10% ethyl acetate in hexane as the eluent the title compound was obtained as an oil (1g, 79%). ¹H-NMR (300 MHz, CDCl₃): δ 0.44-0.54(m, 4H), 1.27(s, 6H), 1.38 (t, *J* = 7Hz, 3H), 1.73(m, 1H), 2.62(s, 2H), 3.76(s, 2H), 4.35 (q, *J* = 7.1Hz, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.74 (dd, *J* = 1.7, 7.9Hz, 1H), 7.97(d, *J* = 1.8Hz, 1H).

2-Cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (Intermediate 24)

A stirred cooled (-78⁰C) solution of ethyl-2-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro isoquinoline-6-carboxylate (Intermediate 23, 1g, 3.66mmol) in anhydrous dichloromethane (20mL) under argon was treated with a 1M solution of di-*iso*-butyl aluminum hydride in dichloromethane (10mL) and the reaction mixture was warmed to -20⁰C over 1h. It was then quenched with saturated aqueous ammonium chloride solution and diluted

1 with dichloromethane and filtered over a bed of celite. The phases were
2 separated and the aqueous phase was extracted with dichloromethane (x1).
3 The combined organic extract was dried over anhydrous sodium sulfate,
4 filtered and evaporated in *vacuo* to afford the title compound as a viscous oil
5 (0.74g, 87%).

6 ¹H-NMR (300 MHz, CDCl₃): δ 0.45-0.53(m, 4H), 1.25(s, 6H), 1.72-1.82(m,
7 2H), 2.61(s, 2H), 3.73(s, 2H), 4.61 (d, *J* = 5Hz, 2H), 6.98(d, *J* = 7.9Hz, 1H),
8 7.07 (dd, *J* = 1.5, 7.6Hz, 1H), 7.27(s, 1H).

9 2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde
10 **(Intermediate 25)**

11 A solution of 2-cyclopropyl-6-hydroxymethyl-4,4-dimethyl-1,2,3,4-
12 tetrahydroisoquinoline (**Intermediate 24**, 0.74g, 3.2mmol) in
13 dichloromethane (10mL) and acetonitrile (2.5mL) was treated sequentially
14 with 4A⁰ molecular sieves powder (1.06g), tetra-*n*-propyl ammonium
15 perruthenate (0.050g, 0.14mmol) and N-methyl morpholine N-oxide (1.1g,
16 9.8mmol). After stirring at ambient temperature for 0.5h, it was diluted with
17 5mL of hexane and subjected to flash column chromatography over silica gel
18 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford
19 the title compound as an oil (0.27g, 37%).

20 ¹H-NMR (300 MHz, CDCl₃):δ 0.44-0.56(m, 4H), 1.30(s, 6H), 1.79(m, 1H),
21 2.66(s, 2H), 3.82(s, 2H), 7.17(d, *J* = 7.9Hz, 1H), 7.60 (dd, *J* = 1.6, 7.9Hz,
22 1H), 7.82(d, *J* = 1.8Hz, 1H), 9.95 (s, 1H).

23 6-(2,2-Dibromo-vinyl)-2-cyclopropyl-4,4-dimethyl-1,2,3,4-
24 tetrahydroisoquinoline (**Intermediate 26**)

25 A stirred, cooled (ice-bath) solution of triphenyl phosphine (0.53g,
26 2mmol) in anhydrous dichloromethane was treated with carbon tetrabromide
27 (0.35g, 1mmol) under argon. After 0.5h, a solution of 2-cyclopropyl-4,4-
28 dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde (**Intermediate**

1 25, 0.13g, 0.57mmol) in dichloromethane (2mL) was cannulated into the
2 reaction mixture. After 1.5h between 0°C and 10°C, the reaction mixture
3 was subjected to flash column chromatography over silica gel (230-400
4 mesh) using 3-5% ethyl acetate in hexane as the eluent to afford the title
5 compound as a viscous, pale yellow oil (0.18g, 82%).
6 ¹H-NMR (300 MHz, CDCl₃): δ 0.49-0.57(m, 4H), 1.31(s, 6H), 1.80(m, 1H),
7 2.67(s, 2H), 3.77(s, 2H), 7.04(d, *J* = 7.9Hz, 1H), 7.29 (dd, *J* = 1.7, 7.9Hz,
8 1H), 7.49 (s, 1H), 7.50(d, *J* = 1.7Hz, 1H).

9 2-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline
10 **(Intermediate 27)**

11 A stirred, cooled (-78°C) solution of 6-(2,2-dibromo-vinyl)-2-
12 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-6-carboxaldehyde
13 (**Intermediate 26**, 0.18g, 0.47mmol) in tetrahydrofuran (2mL) was treated
14 with 1.6M solution of *n*-butyl lithium (0.6mL, 0.96mmol) under argon. The
15 reaction mixture was allowed to warm to -20°C over 1.5h, quenched with
16 saturated aqueous ammonium chloride solution and extracted with diethyl
17 ether (x2). The combined organic phase was dried over anhydrous
18 magnesium sulfate, filtered and evaporated in *vacuo* to afford the title
19 compound as an oil (0.1g, 94%).

20 ¹H-NMR (300 MHz, CDCl₃): δ 0.47-0.55(m, 4H), 1.28(s, 6H), 1.77(m, 1H),
21 2.63(s, 2H), 3.05(s, 1H), 3.67(s, 2H), 6.98(d, *J* = 7.6Hz, 1H), 7.26 (dd, *J* =
22 1.5, 7.9Hz, 1H), 7.46(d, *J* = 1.5Hz, 1H).

23 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
24 2-fluoro-phenyl]-acetic acid ethyl ester (**Compound 21, General Formula**
25 **3**)

26 Following general procedure F and using 2-cyclopropyl-6-ethynyl-
27 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,

1 0.571mmol), 2-fluoro-4-iodo phenyl acetic acid ethyl ester (**Reagent C**,
2 0.16g, 0.52mmol), triethyl amine (0.8mL), anhydrous tetrahydrofuran (2mL),
3 copper(I)iodide (0.051g, 0.27mmol) and
4 dichlorobis(triphenylphosphine)palladium(II) (0.1g, 0.14mmol) followed by
5 flash column chromatography over silica gel (230-400 mesh) using 10%
6 ethyl acetate in hexane as the eluent, 0.1g of the title compound was obtained
7 as an oil. It was further purified by preparative normal phase HPLC on a
8 partisil-10 silica column using 10% ethyl acetate in hexane as the mobile
9 phase (0.055g, 24%).

10 ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.51(m, 4H), 1.26(t, *J* = 7.3Hz, 3H),
11 1.27(s, 6H), 1.75(m, 1H), 2.61(s, 2H), 3.66(s, 2H), 3.74(s, 2H), 4.18 (q, *J* =
12 7.3Hz, 2H), 6.97 (d, *J* = 7.9Hz, 1H), 7.20-7.29(m, 4H), 7.45(d, *J* = 1.5Hz,
13 1H).

14 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
15 2-fluoro-phenyl]-acetic acid (**Compound 22, General Formula 3**)

16 Following general procedure J and using [4-(2-cyclopropyl-4,4-
17 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-ylethynyl)-2-fluoro-phenyl]-acetic
18 acid ethyl ester (**Compound 21**, 0.055g, 0.135mmol), methanol (2mL),
19 tetrahydrofuran (4mL), water (1mL) and lithium hydroxide monohydrate
20 (0.117g, 2.97mmol) the title compound was obtained as a pale yellow solid
21 foam (0.040g, 78%).

22 ¹H-NMR (300 MHz, CDCl₃): δ 0.52-0.65(m, 4H), 1.27(s, 6H), 1.84(m, 1H),
23 2.71(s, 2H), 3.61(s, 2H), 3.85(s, 2H), 6.98(d, *J* = 7.9Hz, 1H), 7.06 (t, *J* =
24 7.6Hz, 1H), 7.17-7.25(m, 3H), 7.43(d, *J* = 1.2Hz, 1H), 8.60-9.00(br s, 1H).

25 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
26 phenyl]-acetic acid methyl ester (**Compound 23, General Formula 3**)

1 Following general procedure F and using 2-cyclopropyl-4,4-dimethyl-
2 6-ethynyl-1,2,3,4-tetrahydro-isoquinoline(**Intermediate 27**, 0.13g,
3 0.571mmol), 4-iodo phenyl acetic acid methyl ester (**Reagent B**, 0.16g,
4 0.58mmol), triethyl amine (0.5mL), anhydrous tetrahydrofuran (2mL),
5 copper(I)iodide (0.04g, 0.21mmol) and
6 dichlorobis(triphenylphosphine)palladium(II) (0.12g, 0.17mmol) followed by
7 flash column chromatography over silica gel (230-400 mesh) using 10%
8 ethyl acetate in hexane as the eluent, 0.05g of the title compound was
9 obtained as an oil. It was further purified by preparative normal phase
10 HPLC on a partisil-10 silica column using 10% ethyl acetate in hexane as the
11 mobile phase (0.01g, 6%).
12 ¹H-NMR (300 MHz, CDCl₃): δ 0.42-0.58(m, 4H), 1.29(m, 6H), 1.79(m, 1H),
13 2.64(s, 2H), 3.67(s, 3H), 3.72(s, 2H), 3.77(s, 2H), 7.09 (d, *J* = 7.9Hz, 1H),
14 7.28(dd, *J* = 1.5, 7.9Hz, 1H), 7.36 (d, *J* = 7.9Hz, 2H), 7.50 (d, *J* = 1.6Hz,
15 1H), 7.51(d, *J* = 7.9Hz, 2H).
16 [4-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethynyl]-
17 phenyl]-acetic acid (**Compound 24**, General Formula 3)

18 Following general procedure J and using [4-(2-cyclopropyl-4,4-
19 dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-ylethynyl)-phenyl]-acetic acid
20 methyl ester (**Compound 23**, 0.01g, 0.027mmol), methanol (1mL),
21 tetrahydrofuran (1mL), water (0.5mL) and lithium hydroxide monohydrate
22 (0.042g, 1mmol) the title compound was obtained as a pale yellow solid
23 foam (0.0065g, 68%).
24 ¹H-NMR (300 MHz, CDCl₃): δ 0.35-0.52(m, 4H), 1.24(s, 6H), 1.74(m, 1H),
25 2.59(s, 2H), 3.64(s, 2H), 3.71(s, 2H), 7.03 (d, *J* = 8.2Hz, 1H), 7.22(dd, *J* =
26 1.4, 7.9Hz, 1H), 7.33 (d, *J* = 8.2Hz, 2H), 7.46 (d, *J* = 8.2Hz, 2H), 7.47(s,
27 1H).

1 1-(*Iso*-propyl-methyl-amino)-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-
2 tetrahydro-naphthalene (Intermediate 28)

3 Following general procedure G and using a solution of 4,4-dimethyl-
4 6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-naphthalene 2-one
5 (**Intermediate 12**, 0.2g, 0.78mmol), dichloromethane (4mL), acetonitrile
6 (2mL), acetic acid (1mL), isopropyl amine (1mL, 11.74mmol) and sodium
7 cyanoborohydride (0.19g, 3.02mmol), after 15days of reaction time and work
8 up afforded an intermediate (0.14g, 60%, 0.47mmol) which was used
9 following general procedure H along with acetone (2mL), potassium
10 carbonate (0.6g, 4.34mmol) and methyl iodide (0.5mL, 8mmol). The crude
11 product after work up was subjected to flash column chromatography over
12 silica gel (230-400 mesh) using 15% ethyl acetate in hexane as the eluent to
13 afford the title compound as a pale yellow oil (0.14g, 95%).

14 ¹H-NMR (300 MHz, CDCl₃): δ 0.001(s, 9H), 0.85 (d, *J* = 6.4Hz, 6H), 0.98
15 (s, 3H), 1.03 (s, 3H), 1.32-1.60 (m, 4H), 1.81(s, 3H), 2.64(heptet, *J* = 6.4Hz,
16 1H), 3.65 (dd, *J* = 6.1, 9.4Hz, 1H), 6.97 (dd, *J* = 1.7, 7.9Hz, 1H), 7.13 (d, *J*
17 = 1.7Hz, 1H), 7.82 (d, *J* = 7.9Hz, 1H).

18 6-Ethynyl-1-(*iso*-propyl-methyl-amino)-4,4-dimethyl-1,2,3,4-tetrahydro-
19 naphthalene (Intermediate 29)

20 Following general procedure E and using 1-(methyl-*iso*-
21 propylamino)-4,4-dimethyl-6-trimethylsilanylethynyl-1,2,3,4-tetrahydro-
22 naphthalene (**Intermediate 28**, 0.14g, 0.45mmol), methanol (5mL),
23 potassium carbonate (0.61g, 4.41mmol) and ethyl acetate the title compound
24 (0.092g, 80%) was obtained as an oil.

25 ¹H-NMR (300 MHz, CDCl₃): δ 1.11(d, *J* = 6.4Hz, 6H), 1.23(s, 3H), 1.28(s,
26 3H), 1.51-1.87 (m, 4H), 2.09(s, 3H), 2.90 (heptet, *J* = 6.4Hz, 1H), 3.00(s,
27 1H), 3.91 (dd, *J* = 5.8, 10.0Hz, 1H), 7.25(dd, *J* = 1.7, 8.2Hz, 1H), 7.41 (d, *J*
28 = 1.7Hz, 1H), 7.70(d, *J* = 8.2Hz, 1H).

1 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
2 naphthalene-2-yl-ethynyl)]-benzoic acid ethyl ester (Compound 25,
3 **General Formula 4)**

4 Following general procedure F and 6-ethynyl-1-(*iso*-propyl-methyl-
5 amino)-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalene (**Intermediate 29**,
6 0.092g, 0.36mmol), ethyl-4-iodo benzoate (**Reagent A**, 0.12g, 0.48mmol),
7 triethyl amine (1mL), tetrahydrofuran (2mL), copper(I)iodide (0.028g,
8 0.14mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.075g,
9 0.11mmol) followed by flash column chromatography over silica gel (230-
10 400 mesh) using 10-15% ethyl acetate in hexane as the eluent the title
11 compound was obtained (0.04g, 27%).

12 ¹H-NMR (300 MHz, CDCl₃): δ 1.12 (d, *J* = 6.5Hz, 6H), 1.27 (s, 3H), 1.31 (s,
13 3H), 1.40 (t, *J* = 7.0Hz, 3H), 1.62-1.89 (m, 4H), 2.10(s, 3H), 2.92 (heptet, *J*
14 = 6.4Hz, 1H), 3.94(dd, *J* = 6.1, 9.7Hz, 1H), 4.38(q, *J* = 7.1Hz, 2H), 7.31(dd,
15 *J* = 1.4, 8.2Hz, 1H), 7.46 (d, *J* = 1.7Hz, 1H), 7.58 (d, *J* = 8.2Hz, 2H),
16 7.75(d, *J* = 8.2Hz, 1H), 8.01(d, *J* = 8.2Hz, 2H).

17 4-[5-(*Iso*-propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-
18 naphthalene-2-yl-ethynyl)]-benzoic acid (Compound 26, General Formula
19 **4)**

20 Following general procedure I and using 4-[5-(*iso*-propyl-methyl-
21 amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-ylethynyl)]-benzoic
22 acid ethyl ester (**Compound 25**, 0.04g, 0.01mmol), ethanol (2mL),
23 tetrahydrofuran (1mL) and 1M aqueous sodium hydroxide solution (1mL)
24 followed by recrystallization from diethylether-hexane, the title compound
25 was obtained as an off-white solid (0.010g, 27%).

26 ¹H-NMR (300 MHz, CDCl₃): δ 1.30(d, *J* = 6.0Hz, 6H), 1.31(s, 9H), 1.67-
27 1.98(m, 4H), 2.35 (s, 3H), 3.19 (heptet, *J* = 6.4Hz, 1H), 4.36 (t, *J* = 7.6Hz,

1 1H), 7.28(dd, $J = 1.4$, 8.2Hz, 1H), 7.48 (d, $J = 1.4$ Hz, 1H), 7.55 (d, $J =$
2 8.2Hz, 2H), 7.81 (d, $J = 8.2$ Hz, 1H), 8.05 (d, $J = 8.2$ Hz, 2H).

3 [4-(2,2,4,4-Tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid methyl
4 ester (Compound 27, General Formula 8)

5 Following general procedure F and using 6-ethynyl-2,2,4,4-
6 tetramethylchroman (synthesis described in U.S. Patent Nos. 5,045,551 and
7 5,616,597 incorporated herein by reference) (0.060g, 0.28mmol), methyl-4-
8 iodo phenyl acetate (**Reagent B**, 0.078g, 0.28mmol), triethyl amine (4mL),
9 tetrahydrofuran (4mL), copper(I)iodide (0.030g, 0.16mmol) and
10 dichlorobis(triphenylphosphine)palladium(II) (0.11g, 0.16mmol) followed by
11 flash column chromatography over silica gel (230-400 mesh) using 5-10 %
12 ethyl acetate in hexane as the eluent the title compound was obtained
13 (0.047g, 46%).

14 ^1H NMR (300 MHz, CDCl_3): δ 7.48-7.45 (m, 3H), 7.25-7.23 (m, 3H), 6.75
15 (d, 1H, $J = 8.2$ Hz), 3.70 (s, 3H), 3.62 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35
16 (s, 6H).

17 GENERAL PROCEDURE L: [4-(2,2,4,4-Tetramethyl-chroman-6-yl-
18 ethynyl) phenyl] acetic acid (Compound 28, General Formula 8)

19 A solution of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl]
20 acetic acid methyl ester (**Compound 27**, 0.047g, 0.13mmol) in 5mL of
21 methanol was treated with 1M sodium hydroxide solution (2mL) and heated
22 at 55°C for 2h. The volatiles were distilled off in *vacuo* and the residue was
23 acidified with 10% hydrochloric acid and extracted with ethyl acetate (x2).
24 The combined organic phase was washed with brine (x1), dried over
25 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue
26 which was purified by preparative reverse phase HPLC using 10% water in
27 acetonitrile as the mobile phase to afford the title compound (0.034g, 82%).

1 ¹H NMR (300 MHz, CDCl₃): δ 7.49-7.45 (m, 3H), 7.26-7.22 (m, 3H), 6.75
2 (d, 1H, *J* = 8.2Hz), 3.65 (s, 2H), 1.84 (s, 2H), 1.36 (s, 6H), 1.35 (s, 6H).
3 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl
4 ester (Compound 29, General Formula 8)

5 Following general procedure F and using 6-ethynyl-2,2,4,4-
6 tetramethylchroman (0.11g, 0.51mmol), methyl-2-fluoro-4-iodo-benzoate
7 (Reagent G, 0.14g, 0.51mmol), triethyl amine (5mL),
8 tetrahydrofuran(10mL), copper(I)iodide(0.030g, 0.16mmol) and
9 dichlorobis(triphenylphosphine)palladium(II) (0.110g, 0.16mmol) followed
10 by flash column chromatography over silica gel (230-400 mesh) using 5-10
11 % ethyl acetate in hexane as the eluent, the title compound was obtained
12 (0.14g, 79%).

13 ¹H NMR (300 MHz, CDCl₃): δ 7.82 (t, 1H, *J* = 7.9Hz), 7.39 (d, 1H, *J* =
14 1.8Hz), 7.25-7.16 (m, 3H), 6.69 (d, 1H, *J* = 8.2Hz), 3.85 (s, 3H), 1.77 (s,
15 2H), 1.29 (s, 6H), 1.28 (s, 6H).

16 2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
17 (Compound 30, General Formula 8)

18 Following general procedure L and using 2-fluoro-4-(2,2,4,4-
19 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid methyl ester (Compound
20 29, 0.14g, 0.4mmol), 5mL of methanol and 1M sodium hydroxide solution
21 (2mL) followed by recrystallization from ethyl acetate, the title compound
22 was obtained (0.083g, 58%).

23 ¹H NMR (300 MHz, CD₃COCD₃): δ 8.00 (t, 1H, *J* = 7.8Hz), 7.63 (d, 1H, *J* =
24 2.1Hz), 7.45 (dd, 1H, *J* = 1.5, 7.9Hz), 7.38 (dd, 1H, *J* = 1.5, 11.4Hz), 7.32
25 (dd, 1H, *J* = 2.1, 8.2Hz), 6.81 (d, 1H, *J* = 8.5Hz), 1.92 (s, 2H), 1.41 (s, 6H),
26 1.38 (s, 6H).

1 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
2 ethyl ester (Compound 31, General Formula 8)

3 Following general procedure F and using 6-ethynyl-2,2,4,4-
4 tetramethylchroman (0.204g, 0.95mmol), ethyl-2-fluoro-4-iodo phenyl
5 acetate (**Reagent C**, 0.263g, 0.86mmol), triethyl amine, tetrahydrofuran,
6 copper(I)iodide (0.025g, 0.13mmol) and
7 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed
8 by flash column chromatography over silica gel (230-400 mesh) using 5-10
9 % ethyl acetate in hexane as the eluent, the title compound was obtained
10 (0.21g, 62%).

11 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 1H, *J* = 2.1Hz), 7.25-7.21 (m, 4H),
12 6.69 (d, 1H, *J* = 8.5Hz), 4.16 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 1.82 (s, 2H),
13 1.35 (s, 6H), 1.35 (s, 6H), 1.24 (t, 3H, *J* = 7.2Hz).

14 [2-Fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
15 (Compound 32, General Formula 8)

16 Following general procedure L and using [2-fluoro-4-(2,2,4,4-
17 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid ethyl ester
18 (**Compound 31**, 0.21g, 0.58mmol), 5mL of methanol and 1M sodium
19 hydroxide solution (2mL) followed by flash column chromatography over
20 silica gel (230-400 mesh) using 50% ethyl acetate in hexane, the title
21 compound was obtained as a solid (0.184g, 93%).

22 ¹H NMR (300 MHz, CDCl₃): δ 11.40 (br s, 1H), 7.48 (d, 1H, *J* = 1.8Hz),
23 7.46-7.16 (m, 4H), 6.76 (d, 1H, *J* = 8.2Hz), 3.69 (s, 2H), 1.82 (s, 2H), 1.34
24 (s, 12H).

25 3-Methyl-but-2-enoic acid 4-bromo-phenyl ester:

26 To a stirred, cooled (ice bath) suspension of sodium hydride (2.4g,
27 100mmol) in anhydrous tetrahydrofuran (200mL), 4-bromo phenol (17.3g,
28 100mmol) was added followed by 3,3,-dimethyl acryloyl chloride (11.14mL,

1 100mmol). After 4hours at ambient temperature, the reaction mixture was
2 poured into brine and extracted with diethyl ether (x2). The combined
3 organic phase was dried over anhydrous sodium sulfate, filtered and
4 evaporated in *vacuo* to afford an oil which was subjected to flash column
5 chromatography over silica gel (230-400 mesh) using 2% ethyl acetate in
6 hexane as the eluent to afford the title compound (15g, 59%).

7 ¹H-NMR (300 MHz, CDCl₃):δ 2.00(s, 3H), 2.23(s, 3H), 5.89(s, 1H), 7.00(d,
8 *J* = 8.8Hz, 2H), 7.49(d, *J* = 8.8Hz, 2H).

9 6-Bromo-4,4-dimethyl-chroman-2-one:

10 A solution of 3-methyl-but-2-enoic acid 4-bromo-phenyl ester (7g,
11 27.6mmol) in anhydrous dichloromethane (200mL) was cooled (ice bath)
12 and treated with aluminum chloride (6.6g, 49.6mmol) and the reaction
13 mixture was stirred overnight at ambient temperature. The reaction mixture
14 was quenched with saturated aqueous sodium bicarbonate solution and
15 extracted with diethyl ether (x2). The combined organic extract was washed
16 with brine (x1), dried over anhydrous sodium sulfate, filtered and
17 evaporated in *vacuo* to afford an oil which was purified by flash column
18 chromatography over silica gel (230-400 mesh) using 2.5% ethyl acetate in
19 hexane as the eluent to afford the title compound (4.2g, 57%).

20 ¹H-NMR (300 MHz, CDCl₃):δ 1.36(s, 6H), 2.62(s, 2H), 6.95(d, *J* = 8.5Hz,
21 1H), 7.37(dd, *J* = 2.4, 8.5Hz, 1H), 7.43(d, *J* = 2.3Hz, 1H).

22 4-Bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol:

23 A solution of 6-bromo-4,4-dimethyl-chroman-2-one (1g, 3.92mmol)
24 in anhydrous tetrahydrofuran (20mL) was treated with 3M solution of ethyl
25 magnesium bromide (2.6mL) and stirred at ambient temperature for 2hours.
26 The reaction mixture was poured into cold dilute hydrochloric acid and
27 extracted with ethyl acetate (x2). The combined organic extract was dried

1 over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to afford a
2 residue which was subjected to flash column chromatography over silica gel
3 (230-400 mesh) using 10% ethyl acetate in hexane as the eluent to afford the
4 title compound as a pale yellow solid (1.1g, 100%).

5 ¹H-NMR (300 MHz, CDCl₃): δ 1.14(s, 6H), 1.44(s, 6H), 2.20(s, 2H), 6.49(d,
6 *J* = 8.4Hz, 1H), 7.15(dd, *J* = 2.4, 8.5Hz, 1H), 7.37(d, *J* = 2.4Hz, 1H).

7 6-Bromo-2,2,4,4-tetramethyl-chroman:

8 A solution of 4-bromo-2-(3-hydroxy-1,1,3-trimethyl-butyl)-phenol
9 (1.1g, 3.92mmol) and *p*-toluene sulfonic acid (0.744g, 3.92mmol) in benzene
10 (20mL) was refluxed overnight. The reaction mixture cooled to ambient
11 temperature, filtered on silica gel and washed with 10% ethyl acetate in
12 hexane. The filtrate and washings were evaporated in *vacuo* to an oil which
13 was subjected to flash column chromatography over silica gel (230-400
14 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title
15 compound as a pale yellow oil (0.84g, 80%).

16 ¹H-NMR (300 MHz, CDCl₃): δ 1.34(s, 6H), 1.35(s, 6H), 1.82(s, 2H), 6.68(d,
17 *J* = 8.4Hz, 1H), 7.16(dd, *J* = 2.7, 8.7Hz, 1H), 7.37(d, *J* = 2.6Hz, 1H).

18 The synthesis of this compound, as described here, is in close analogy
19 to the synthesis of 6-bromo-2,2,4,4-tetramethylthiochroman, as described in
20 United States Patent No. 5,045,551

21 2,2,4,4-tetramethyl-6-(2-trimethylsilyl)ethynyl chroman:

22 Following general procedure D and using 6-bromo-2,2,4,4-
23 tetramethyl chroman (0.5g, 1.87mmol), triethyl amine (5mL), anhydrous
24 tetrahydrofuran (15mL), copper(I)iodide (0.107g, 0.156mmol), trimethylsilyl
25 acetylene (1.84g, 18.7mmol) and
26 dichlorobis(triphenylphosphine)palladium(II) (0.39g, 0.56mmol) the title
27 compound was obtained as a brown oil (0.61g, 100%).

1 ¹H NMR (300 MHz, CDCl₃): δ 7.43 (d, 1H, *J* = 2.1Hz), 7.23 (dd, 1H, *J* =
2 7.9, 2.1Hz), 6.73 (d, 1H, *J* = 8.2Hz), 1.83 (s, 2H), 1.36 (s, 12H), 0.28 (s, 9H).

3 6-Ethynyl-2,2,4,4-tetramethyl chroman:

4 Following general procedure E and using 2,2,4,4-tetramethyl-6-(2-
5 trimethylsilyl)ethynyl chroman (0.61g, 1.87mmol), potassium carbonate
6 (1.9g, 13.74mmol) and methanol the title compound was obtained (0.4g,
7 90%).

8 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* =
9 7.9, 2.1Hz), 6.76 (d, 1H, *J* = 8.2Hz), 3.01 (s, 1H), 1.85 (s, 2H), 1.37 (s, 6H),
10 1.36 (s, 6H).

11 An alternative synthesis for this compound is described in United
12 States Patent Nos. 5,045,551 and 5,616,597

13 GENERAL PROCEDURE M: 6-Bromo-2,2,4,4-tetramethyl-chroman-8-
14 carbaldehyde (Intermediate 30)

15 A stirred, cooled (ice bath) solution of 6-bromo-2,2,4,4-tetramethyl
16 chroman, (0.5g, 1.865mmol) in anhydrous dichloromethane (5mL) was
17 treated with a 1M solution (1.86mL, 1.86mmol) of titanium tetrachloride in
18 dichloromethane followed by α,α-dichloro methyl ether (0.214g,
19 1.865mmol). The reaction mixture was allowed to warm to ambient
20 temperature for 4h. The reaction mixture was diluted with diethyl ether,
21 washed with brine (x1) and dried over anhydrous sodium sulfate, filtered and
22 evaporated in *vacuo* to a residue which was subjected to flash column
23 chromatography over silica gel (230-400 mesh) using 5% ethyl acetate in
24 hexane to afford the title compound as a yellow solid (0.52g, 94%).

25 ¹H NMR (300 MHz, CDCl₃): δ 10.38 (s, 1H), 7.72 (d, 1H, *J* = 2.6Hz), 7.57
26 (d, 1H, *J* = 2.6Hz), 1.88 (s, 2H), 1.41 (s, 6H), 1.36 (s, 6H).

1 GENERAL PROCEDURE N: 6-Bromo-8-vinyl-2,2,4,4-tetramethyl-
2 chroman (Intermediate 31)

3 A solution of methylidene triphenyl phosphorane [generated from
4 methyl triphenylphosphonium bromide (7g, 20mmol) and (11.8mL, 19mmol)
5 of a 1.6M solution of *n*-butyl lithium in hexanes] was added 6-bromo-
6 2,2,4,4-tetramethyl chroman-8-carbaldehyde (**Intermediate 30**, 0.52g,
7 1.75mmol). After 1h the reaction mixture was diluted with hexane, washed
8 with brine (x1), dried over anhydrous sodium sulfate, filtered and evaporated
9 in *vacuo* to a clear oil which was subjected to flash column chromatography
10 over silica gel (230-400 mesh) using 2% ethyl acetate in hexane as the eluent
11 to afford the title compound as a clear oil (0.37g, 72%).

12 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 1H, *J* = 2.5Hz), 7.33 (d, 1H, *J* =
13 2.5Hz), 7.03 (dd, 1H, *J* = 11.3, 17.9Hz), 5.75 (dd, 1H, *J* = 1.4, 17.9Hz), 5.30
14 (dd, 1H, *J* = 1.4, 11.3Hz), 1.85 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

15 GENERAL PROCEDURE O: 6-Bromo-8-cyclopropyl-2,2,4,4-tetramethyl
16 chroman (Intermediate 32)

17 A stirred, cooled (-30°C) solution of 6-bromo-8-vinyl-2,2,4,4-
18 tetramethyl chroman (**Intermediate 31**, 0.37g, 1.26mmol) in diethyl ether
19 was treated with a solution of diazomethane in diethyl ether and catalytic
20 amount of palladium (II)acetate (~30mg). The reaction mixture was allowed
21 to warm to ambient temperature and subjected to flash column
22 chromatography over silica gel (230-400 mesh) using 2% ethyl acetate in
23 hexane as the eluent to afford the title compound as a clear, pale yellow oil
24 (0.376g, 97%).

25 ¹H NMR (300 MHz, CDCl₃): δ 7.17 (d, 1H, *J* = 2.3Hz), 6.73 (d, 1H, *J* =
26 2.6Hz), 2.19-2.16 (m, 1H), 1.83 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H), 0.94-0.88
27 (m, 2H), 0.64-0.59 (m, 2H).

1 8-Cyclopropyl-6-trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman

2 **(Intermediate 33)**

3 Following general procedure D and using 6-bromo-8-cyclopropyl-
4 2,2,4,4-tetramethyl chroman (**Intermediate 32**, 0.376g, 1.22mmol),
5 (trimethylsilyl)acetylene (4mL, 28mmol), triethyl amine (3mL), anhydrous
6 tetrahydrofuran (5mL), copper(I)iodide (0.025g, 0.13mmol) and
7 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title
8 compound was obtained as an oil (0.173g, 43%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.36 (d, 1H, *J* = 2.2Hz), 6.90 (d, 1H, *J* =
10 1.9Hz), 2.31-2.22 (m, 1H), 1.96 (s, 2H), 1.49 (s, 6H), 1.46 (s, 6H), 1.05-0.88
11 (m, 2H), 0.78-0.72 (m, 2H), 0.37 (s, 9H).

12 8-Cyclopropyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 34**)

13 Following general procedure E and using 8-cyclopropyl-6-
14 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 33**,
15 0.17g, 0.68mmol), methanol and potassium carbonate (0.2g, 1.47mmol) the
16 title compound was obtained as an oil (0.064g, 47%).

17 ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, 1H, *J* = 1.9Hz), 6.92 (d, 1H, *J* =
18 1.9Hz), 3.08 (s, 1H), 2.32-2.23 (m, 1H), 1.96 (s, 2H), 1.50 (s, 6H), 1.46 (s,
19 6H), 1.05-0.99 (m, 2H), 0.77-0.72 (m, 2H).

20 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
21 ethyl ester (**Compound 33, General Formula 8**)

22 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
23 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.1g, 0.38mmol), ethyl-4-
24 iodo-benzoate (**Reagent A**, 0.1g, 0.34mmol), triethyl amine (5mL),
25 tetrahydrofuran(10mL), copper(I)iodide(0.025g, 0.13mmol) and
26 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) followed
27 by flash column chromatography over silica gel (230-400 mesh) using 5-10

1 % ethyl acetate in hexane as the eluent, the title compound was obtained
2 (0.135g, 89%).
3 ¹H NMR (300 MHz, CDCl₃): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* =
4 8.2Hz), 7.30 (d, 1H, *J* = 1.8Hz), 6.84 (d, 1H, *J* = 2.0Hz), 4.38 (q, 2H, *J* =
5 6.9Hz), 2.22-2.12 (m, 1H), 1.85 (s, 2H), 1.40 (t, 3H, *J* = 6.9Hz), 1.38 (s, 6H),
6 1.36 (s, 6H), 0.92-0.88 (m, 2H), 0.67-0.62 (m, 2H).

7 4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid
8 **(Compound 34, General Formula 8)**

9 Following general procedure L and using 4-(8-cyclopropyl-2,2,4,4-
10 tetramethyl-chroman-6-yl-ethynyl)-benzoic acid ethyl ester (**Compound 33**,
11 0.135g, 0.34mmol), 5mL of methanol and 1M sodium hydroxide solution
12 (2mL) followed by preparative reverse phase HPLC using 10% water in
13 acetonitrile as the mobile phase, the title compound was obtained as a solid
14 (0.093g, 73%).

15 ¹H NMR (300 MHz, CDCl₃): δ 11.26 (br s, 1H), 8.08 (d, 2H, *J* = 8.2Hz),
16 7.59 (d, 2H, *J* = 8.2Hz), 7.31 (d, 1H, *J* = 1.8Hz), 6.85 (d, 1H, *J* = 2.1Hz),
17 2.22-2.13 (m, 1H), 1.85 (s, 2H), 1.38 (s, 6H), 1.36 (s, 6H), 0.95-0.87 (m,
18 2H), 0.68-0.63 (m, 2H).

19 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic
20 acid methyl ester (**Compound 35, General Formula 8**)

21 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
22 2,2,4,4-tetramethylchroman (**Intermediate 34**, 0.096g, 0.38mmol), methyl-
23 4-iodo phenyl acetate (**Reagent B**, 0.094g, 0.34mmol), triethyl amine (3mL),
24 tetrahydrofuran (3mL), copper(I)iodide (0.025g, 0.13mmol) and
25 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title
26 compound was obtained (0.137g, 90%). ¹H NMR (300 MHz, CDCl₃): δ 7.47
27 (d, 2H, *J* = 7.9Hz), 7.29 (d, 1H, *J* = 1.8Hz), 7.24 (d, 2H, *J* = 7.9 Hz), 6.82 (d,

1 1H, $J = 2.1\text{Hz}$), 3.70 (s, 3H), 3.63 (s, 2H), 2.22-2.13 (m, 1H), 1.85 (s, 2H),
2 1.38 (s, 6H), 1.36 (s, 6H), 0.94-0.86 (m, 2H), 0.68-0.63 (m, 2H).
3 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic
4 acid (Compound 36, General Formula 8)

5 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-
6 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester
7 (Compound 35, 0.137g, 0.30mmol), 5mL of methanol and 1M sodium
8 hydroxide solution (2mL) followed by preparative reverse phase HPLC
9 using 10% water in acetonitrile as the mobile phase, the title compound was
10 obtained as a solid (0.11g, 80%).

11 ^1H NMR (300 MHz, CDCl_3): δ 11.56 (br s, 1H), 7.47 (d, 2H, $J = 8.9\text{Hz}$),
12 7.28 (d, 1H, $J = 1.9\text{Hz}$), 7.23 (d, 2H, $J = 8.5\text{Hz}$), 6.82 (d, 1H, $J = 1.9\text{Hz}$),
13 3.62 (s, 2H), 2.21-2.12 (m, 1H), 1.83 (s, 2H), 1.36 (s, 6H), 1.34 (s, 6H), 0.93-
14 0.82 (m, 2H), 0.72-0.62 (m, 2H).

15 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-
16 fluorophenyl] acetic acid ethyl ester (Compound 37, General Formula 8)

17 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
18 2,2,4,4-tetramethylchroman (Intermediate 34, 0.096g, 0.38mmol), ethyl-2-
19 fluoro-4-iodo phenyl acetate (Reagent C, 0.104g, 0.34mmol), triethyl amine
20 (3mL), tetrahydrofuran (3mL), copper(I)iodide (0.020g, 0.1mmol) and
21 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) the title
22 compound was obtained (0.14g, 85%).

23 ^1H NMR (300 MHz, CDCl_3): δ 7.31 (d, 1H, $J = 1.9\text{Hz}$), 7.29-7.21 (m, 3H),
24 6.85 (d, 1H, $J = 1.9\text{Hz}$), 4.20 (q, 2H, $J = 7.1\text{Hz}$), 3.68 (s, 2H), 2.24-2.14 (m,
25 1H), 1.87 (s, 2H), 1.40 (s, 6H), 1.38 (s, 6H), 1.28 (t, 3H, $J = 7.1\text{Hz}$), 0.96-
26 0.85 (m, 2H), 0.70-0.64 (m, 2H).

1 [4-(8-Cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-2-
2 fluorophenyl] acetic acid (Compound 38, General Formula 8)

3 Following general procedure L and using [4-(8-cyclopropyl-2,2,4,4-
4 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid ethyl ester
5 (Compound 37, 0.14g, 0.323mmol), 5mL of methanol and 1M sodium
6 hydroxide solution (2mL) followed by reverse phase HPLC using 10% water
7 in acetonitrile as the mobile phase, the title compound was obtained as a
8 solid (0.110g, 80%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, 1H, *J* = 2.1Hz), 7.27-7.17 (m, 3H),
10 6.82 (d, 1H, *J* = 1.8Hz), 3.70 (s, 2H), 2.21-2.11 (m, 1H), 1.84 (s, 2H), 1.37
11 (s, 6H), 1.35 (s, 6H), 0.94-0.87 (m, 2H), 0.67-0.62 (m, 2H).

12 GENERAL PROCEDURE P: 6-Bromo-4,4-dimethyl-2-methylene chroman
13 (Intermediate 35)

14 A stirred, cooled (ice bath) solution of 6-bromo-4,4-dimethyl-
15 chroman-2-one available in accordance with U.S. Patent No. 5,399,561
16 incorporated herein by reference (1g, 3.92mmol) in 8mL of anhydrous
17 tetrahydrofuran was treated with a 0.5 M solution of μ -chloro- μ -methylene-
18 [bis(cyclopentadienyl)titanium]dimethylaluminum (Tebbe reagent) in
19 toluene (8.23mL, 4.12mmol). After 10 minutes, the reaction mixture was
20 poured into ice-water mixture containing 50mL of 1M sodium hydroxide and
21 extracted with hexane. The hexane extract was washed with brine (x1),
22 filtered over a bed of celite and evaporated in *vacuo* to an oil which was
23 subjected to flash column chromatography over silica gel (230-400 mesh)
24 using hexane as the eluent to afford the title compound (0.74g, 74%) as a
25 clear oil.

1 ¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =
2 2.3, 8.5Hz), 6.77 (d, 1H, *J* = 8.0Hz), 4.61 (d, 1H, *J* = 0.73Hz), 4.17 (d, 1H, *J*
3 = 0.73Hz), 2.33 (s, 2H), 1.27 (s, 6H).

4 GENERAL PROCEDURE Q: 6-Bromo-3,4-dihydro-4,4-dimethylspiro[2H-
5 1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**)

6 A solution of diethyl zinc in hexane (1M, 7.1mL) was treated with
7 diiodomethane (1.89g, 7.1mmol). After 5 minutes, a solution of 6-bromo-
8 4,4-dimethyl-2-methylene chroman (**Intermediate 35**, 0.44g, 1.77mmol) in
9 3mL of hexane was added and the solution was refluxed for 1h. The
10 reaction mixture was then cooled to ambient temperature, diluted with
11 hexane, washed with brine (x1), dried over anhydrous sodium sulfate,
12 filtered and evaporated in *vacuo* to a residue which was subjected to flash
13 column chromatography over silica gel (230-400 mesh) using hexane as the
14 eluent to obtain the title compound (0.44g, 93%).

15 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 1H, *J* = 2.3Hz), 7.23 (dd, 1H, *J* =
16 2.3, 8.5Hz), 6.70 (d, 1H, *J* = 8.0Hz), 1.96 (s, 2H), 1.47 (s, 6H), 1.09-1.05 (m,
17 2H), 0.74-0.70 (m, 2H).

18 3,4-Dihydro-4,4-dimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-
19 benzopyran-2,1'-cyclopropane] (**Intermediate 37**)

20 Following general procedure D and using 6-bromo-3,4-dihydro-4,4-
21 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 36**,
22 0.44g, 1.65mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),
23 copper(I)iodide (0.95g, 0.5mmol), trimethylsilyl acetylene (1.62g,
24 16.5mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.4g,
25 0.56mmol), the title compound was obtained as a brown oil (0.4g, 86%).

¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 1.87 (s, 2H), 1.37 (s, 6H), 1.01-0.97 (m, 2H), 0.65-0.61 (m, 2H), 0.26 (s, 9H).

6-Ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**)

Following general procedure E and using 3,4-dihydro-4,4-dimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 37**, 0.4g, 1.42mmol), potassium carbonate (0.98g, 7.1mmol) and methanol, the title compound was obtained as a yellow oil (0.3g, 100%).

¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, 1H, *J* = 2.1Hz), 7.18 (dd, 1H, *J* = 2.1, 8.5Hz), 6.65 (d, 1H, *J* = 8.5Hz), 2.97 (s, 1H), 1.86 (s, 2H), 1.37 (s, 6H), 1.00-0.95 (m, 2H), 0.64-0.59 (m, 2H).

Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 39, General Formula 1**)

Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**, 0.06g, 0.28mmol), ethyl-4-iodo-benzoate (**Reagent A**, 0.086g, 0.31mmol), triethyl amine (4mL), tetrahydrofuran (4mL), copper(I)iodide (0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.118g, 0.17mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 5-10 % ethyl acetate in hexane as the eluent, the title compound was obtained (0.07g, 70%).

¹H NMR (300 MHz, CDCl₃): δ 8.01 (d, 2H, *J* = 8.2Hz), 7.56 (d, 2H, *J* = 8.5Hz), 7.49 (d, 1H, *J* = 2.1Hz), 7.24 (dd, 1H, *J* = 2.1, 8.5Hz), 6.70 (d, 1H, *J* = 8.5Hz), 4.38 (q, 2H, *J* = 7.1Hz), 1.89 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz), 1.02-0.98 (m, 2H), 0.67-0.62 (m, 2H).

1 Benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
2 cyclopropane]-6-yl)ethynyl]- (Compound 40, General Formula 1)

3 Following general procedure L and using benzoic acid, 4-[(3,4-dihydro-4,4-
4 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester
5 (Compound 39, 0.07g, 0.196mmol), 5mL of ethanol and 1M sodium
6 hydroxide solution (2mL) followed by preparative reverse phase HPLC
7 using 10% water in acetonitrile as the mobile phase, the title compound was
8 obtained as a solid (0.034g, 52%).

9 ¹H NMR (300 MHz, CD₃COCD₃): δ 8.05 (d, 2H, J = 8.2Hz), 7.64 (d, 2H, J =
10 8.2Hz), 7.60 (d, 1H, J = 2.1Hz), 7.28 (dd, 1H, J = 2.1, 8.5Hz), 6.73 (d, 1H, J
11 = 8.5Hz), 1.95 (s, 2H), 1.43 (s, 6H), 0.96-0.92 (m, 2H), 0.74-0.71 (m, 2H).

12 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
13 2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (Compound 41, General
14 Formula 1)

15 Following general procedure F and using 6-ethynyl-3,4-dihydro-4,4-
16 dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (Intermediate 38, ,
17 0.060g, 0.28mmol), methyl 4-iodo phenyl acetate (Reagent B, 0.078g,
18 0.28mmol), triethyl amine (4mL), tetrahydrofuran (4mL), copper(I)iodide
19 (0.032g, 0.17mmol) and dichlorobis(triphenylphosphine)palladium(II)
20 (0.118g, 0.17mmol) followed by flash column chromatography over silica
21 gel (230-400 mesh) using 5 % ethyl acetate in hexane as the eluent, the title
22 compound was obtained (0.084g, 84%).

23 ¹H NMR (300 MHz, CDCl₃): δ 7.48-7.45 (m, 3H), 7.26-7.20 (m, 3H), 6.67
24 (d, 1H, J = 8.5Hz), 3.70 (s, 3H), 3.63 (s, 2H), 1.89 (s, 2H), 1.40 (s, 3H), 1.40
25 (s, 3H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).

26 Benzeneacetic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
27 2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 42, Formula 1)

1 A solution of benzenecetic acid, 4-[(3,4-dihydro-4,4-
2 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl
3 ester (**Compound 41**, 0.084g, 0.24mmol) in 5mL of methanol was treated
4 with 1M sodium hydroxide solution (2mL) and heated at 55°C for 2h. The
5 volatiles were distilled off in *vacuo* and the residue was acidified with 10%
6 hydrochloric acid and extracted with ethyl acetate (x2). The combined
7 organic phase was washed with brine (x1), dried over anhydrous sodium
8 sulfate, filtered and evaporated in *vacuo* to a residue which was purified by
9 preparative reverse phase HPLC using 10% water in acetonitrile as the
10 mobile phase to afford the title compound (0.080g, 100%).

11 ¹H NMR (300 MHz, CD₃COCD₃): δ 7.49-7.46 (m, 3H), 7.25 (d, 2H, *J*=
12 8.2Hz), 7.22 (dd, 1H *J*= 2.1, 8.5Hz), 6.68 (d, 1H, *J*= 8.5Hz), 3.66 (s, 2H),
13 1.88 (s, 2H), 1.44 (s, 6H), 1.01-0.97 (m, 2H), 0.67-0.61 (m, 2H).
14 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-
15 2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 43**, General
16 **Formula 1**)

17 Following general procedure F and 6-ethynyl-3,4-dihydro-4,4-
18 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane] (**Intermediate 38**,
19 0.050g, 0.23mmol), methyl-2-fluoro-4-iodo-benzoate (**Reagent G**, 0.069g,
20 0.24mmol), triethyl amine (5mL), tetrahydrofuran(5mL),
21 copper(I)iodide(0.013g, 0.07mmol) and
22 dichlorobis(triphenylphosphine)palladium(II) (0.049g, 0.07mmol) followed
23 by flash column chromatography over silica gel (230-400 mesh) using 5-10
24 % ethyl acetate in hexane as the eluent, the title compound was obtained
25 (0.080g, 100%).

26 ¹H NMR (300 MHz, CDCl₃): δ 7.90 (t, 1H, *J*= 7.9Hz), 7.63 (d, 1H, *J*=
27 1.8Hz), 7.32 (dd, 1H, *J*= 1.5, 8.2Hz), 7.26 (dd, 1H, *J*= 1.5, 11.4Hz), 7.24

1 (dd, 1H, $J = 2.1, 8.5\text{Hz}$), 6.71 (d, 1H, $J = 8.5\text{Hz}$), 1.97 (s, 2H), 1.44 (s, 6H),
2 0.98-0.94 (m, 2H), 0.76-0.71 (m, 2H).

3 2-Fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
4 2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 44, General Formula 1)

5 Following general procedure L and using 2-fluoro-benzoic acid, 4-
6 [(3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
7 yl)ethynyl]-methyl ester (Compound 43, 0.08g, 0.23mmol), 5mL of
8 methanol and 2M sodium hydroxide solution (1mL) followed by flash
9 column chromatography over silica gel (230-400 mesh) using ethyl acetate
10 as the eluent, the title compound was obtained (0.020g, 25%).

11 ^1H NMR (300 MHz, CD_3COCD_3): δ 7.99 (t, 1H, $J = 7.9\text{Hz}$), 7.63 (d, 1H, $J =$
12 2.1Hz), 7.44 (dd, 1H, $J = 1.5, 7.9\text{Hz}$), 7.37 (dd, 1H, $J = 1.5, 11.4\text{Hz}$), 7.31
13 (dd, 1H, $J = 2.1, 8.5\text{Hz}$), 6.75 (d, 1H, $J = 8.2\text{Hz}$), 1.97 (s, 2H), 1.44 (s, 6H),
14 0.98-0.94 (m, 2H), 0.76-0.71 (m, 2H).

15 GENERAL PROCEDURE R: 2,2,4,4-Tetramethyl-chroman-6-carboxylic
16 acid (Intermediate 39)

17 A stirred, cooled (-78°C) solution of 6-bromo-2,2,4,4-tetramethyl
18 chroman (1.2g, 4.47mmol) in 15mL of anhydrous tetrahydrofuran was
19 treated with a 1.7M solution of *tert*-butyl lithium solution in pentane (
20 5.27mL, 8.9mmol). After 10 minutes at -78°C , carbon dioxide (generated
21 from dry ice) was bubbled into the reaction mixture. The reaction mixture
22 was allowed to warm to ambient temperature. The reaction mixture was
23 diluted with ethyl acetate, washed with brine, dried over anhydrous sodium
24 sulfate, filtered and evaporated in *vacuo* to a residue which was subjected to
25 flash column chromatography over silica gel (230-400 mesh) using ethyl
26 acetate as the eluent to afford the title compound as a white solid (1.1g,
27 92%).

¹H NMR (300 MHz, CDCl₃): δ 12.17 (br s, 1H), 8.09 (d, 1H, *J* = 2.1Hz), 7.85 (dd, 1H, *J* = 2.1, 8.5Hz), 6.83 (d, 1H, *J* = 8.2Hz), 1.87 (s, 2H), 1.39 (s, 6H), 1.37 (s, 6H).

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (**Compound 45, General Formula 8**)

A solution of 2,2,4,4-tetramethyl chroman-6-carboxylic acid (0.1g, 0.43mmol) in thionyl chloride (10mL) was refluxed for 2h. The thionyl chloride was evaporated under reduced pressure and the residue was dissolved in 5mL of dichloromethane and treated with triethyl amine (5mL) followed by *tert*-butyl-4-hydroxy phenyl acetate (**Reagent E**, 0.088g, 0.427mmol). After 0.5h, the reaction mixture was subjected to flash column chromatography over silica gel (230-400 mesh) using 5-10% ethyl acetate in hexane as the eluent to afford the title compound (0.1g, 55%).

¹H NMR (300 MHz, CDCl₃): δ 8.15 (d, 1H, *J* = 2.1Hz), 7.93 (dd, 1H, *J* = 2.1, 8.5Hz), 7.33 (d, 2H, *J* = 8.8Hz), 7.16 (d, 2H, *J* = 8.8Hz), 6.88 (d, 1H, *J* = 8.5Hz), 3.54 (s, 2H), 1.89 (s, 2H), 1.45 (s, 9H), 1.41 (s, 6H), 1.40 (s, 6H).

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester (**Compound 46, General Formula 8**)

A solution of 2,2,4,4-tetramethyl-chroman-6-carboxylic acid 4-(*tert*-butoxycarbonylmethyl)phenyl ester (**Compound 45**, 0.1g, 0.23mmol) was treated with 5mL of trifluoroacetic acid and stirred at ambient temperature for 1h. The trifluoroacetic acid was distilled off under reduced pressure and the residue was subjected to preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase to afford the title compound as a white solid (0.045g, 50%).

¹H NMR (300 MHz, CDCl₃): δ 8.13 (d, 1H, *J* = 2.1Hz), 7.92 (dd, 1H, *J* = 2.3, 8.5Hz), 7.35 (d, 2H, *J* = 8.8Hz), 7.17 (d, 2H, *J* = 8.5Hz), 6.87 (d, 1H, *J* = 8.5Hz), 3.68 (s, 2H), 1.89 (s, 2H), 1.41 (s, 6H), 1.39 (s, 6H).

6-Bromo-8-carbaldehyde-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 40**)

Following general procedure M and using 6-bromo-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 36**, 2.3g, 8.65mmol), anhydrous dichloromethane (25mL), 1M solution (8.65mL, 8.65mmol) of titanium tetrachloride in dichloromethane and α,α-dichloromethyl ether (1.09g, 9.52mmol) followed by flash column chromatography using 10% ethyl acetate in hexane as the eluent, the title compound was obtained as a yellow solid (2.06g, 81%).

¹H NMR (300 MHz, CDCl₃): δ 10.20 (s, 1H), 7.69 (d, 1H, *J* = 2.6Hz), 7.58 (d, 1H, *J* = 2.6Hz), 1.92 (s, 2H), 1.40 (s, 6H), 1.09-1.04 (m, 2H), 0.73-0.69 (m, 2H).

6-Bromo-3,4-dihydro-4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane] (**Intermediate 41**)

Following general procedure N and using A solution of methylenetriphenyl phosphorane [generated from methyl triphenylphosphonium bromide (7g, 20mmol) and 1.6M solution of *n*-butyl lithium in hexanes (11.8mL, 19mmol)], 6-bromo-8-carbonyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane](**Intermediate 40**, 2.06g, 7mmol) followed by flash column chromatography over silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title compound was obtained as a clear oil (1.36g, 66%).

¹H NMR (300 MHz, CDCl₃): δ 7.36 (d, 1H, *J* = 2.3Hz), 7.28 (d, 1H, *J* = 2.6Hz), 6.80 (dd, 1H, *J* = 11.1, 17.9Hz), 5.63 (dd, 1H, *J* = 1.2, 17.9Hz), 5.19

1 (dd, 1H, $J = 1.2, 11.1\text{Hz}$), 1.84 (s, 2H), 1.35 (s, 6H), 0.97 (t, 2H, $J = 6.3\text{Hz}$),
2 0.62 (d, 1H, $J = 5.3\text{Hz}$), 0.60 (d, 1H, $J = 6.2\text{Hz}$).

3 6-Bromo-8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
4 2,1'-cyclopropane] (Intermediate 42)

5 Following general procedure O and using A 6-bromo-3,4-dihydro-
6 4,4-dimethyl-8-vinylspiro[2H-1-benzopyran-2,1'-cyclopropane]
7 (Intermediate 41, 1.36g, 4.6mmol), a solution of diazomethane in diethyl
8 ether and palladium (II)acetate (~30mg) followed by flash column
9 chromatography over silica gel (230-400 mesh) using hexane as the eluent,
10 the title compound was obtained as a clear oil (1.38g, 100%).

11 ^1H NMR (300 MHz, CDCl_3): δ 7.19 (d, 1H, $J = 2.2\text{Hz}$), 6.71 (d, 1H, $J =$
12 2.2Hz), 1.99-1.92 (m, 1H), 1.87 (s, 2H), 1.35 (s, 6H), 1.00-0.95 (m, 2H),
13 0.90-0.82 (m, 2H), 0.65-0.54 (m, 4H).

14 8-Cyclopropyl-3,4-dihydro-4,4-dimethyl-6-
15 (trimethylsilyl)ethynylspiro[2H-1-benzopyran-2,1'-cyclopropane]
16 (Intermediate 43)

17 Following general procedure D and 6-bromo-8-cyclopropyl-3,4-
18 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
19 (Intermediate 42, 0.74g, 2.4mmol), (trimethylsilyl)acetylene (4mL,
20 28mmol), triethyl amine (8mL), anhydrous tetrahydrofuran, copper(I)iodide
21 (0.050g, 0.26mmol) and dichlorobis(triphenylphosphine)palladium(II)
22 (0.15g, 0.22mmol), followed by flash column chromatography over silica gel
23 (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent, the title
24 compound was obtained as an oil (0.62g, 80%).

25 ^1H NMR (300 MHz, CDCl_3): δ 7.28 (d, 1H, $J = 1.9\text{Hz}$), 6.77 (d, 1H, $J =$
26 1.9Hz), 2.03-1.94 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.05-0.98 (m, 2H),
27 0.95-0.83 (m, 2H), 0.69-0.59 (m, 4H), 0.27 (s, 9H).

1 8-Cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-
2 2,1'-cyclopropane] (**Intermediate 44**)

3 Following general procedure E, and 8-cyclopropyl-3,4-dihydro-4,4-
4 dimethyl-6-(trimethylsilanyl)ethynylspiro[2H-1-benzopyran-2,1'-
5 cyclopropane] (**Intermediate 43**, 0.62g, 1.9mmol), methanol and potassium
6 carbonate (0.5g, 3.6mmol) followed by flash column chromatography over
7 silica gel (230-400 mesh) using 1-2% ethyl acetate in hexane as the eluent,
8 the title compound was obtained as an oil (0.5g, 100%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.30 (d, 1H, *J* = 1.8Hz), 6.80 (d, 1H, *J* =
10 2.0Hz), 2.97 (s, 1H), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.39 (s, 6H), 1.20-0.90
11 (m, 2H), 0.90-0.84 (m, 2H), 0.75-0.58 (m, 4H).

12 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
13 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**,
14 **General Formula 1**)

15 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
16 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
17 (**Intermediate 44**, 0.11g, 0.43mmol), methyl-4-iodo phenyl acetate
18 (**Reagent B**, 0.114g, 0.41mmol), triethyl amine (5mL), tetrahydrofuran
19 (3mL), copper(I)iodide (0.025g, 0.13mmol) and
20 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), the title
21 compound was obtained as a clear oil (0.096g, 56%).

22 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 2H, *J* = 8.0Hz), 7.31 (d, 1H, *J* =
23 1.9Hz), 7.24 (d, 2H, *J* = 8.2Hz), 6.81 (d, 1H, *J* = 1.9Hz), 3.69 (s, 3H), 3.62
24 (s, 2H), 2.04-1.95 (m, 1H), 1.90 (s, 2H), 1.39 (s, 6H), 1.03-0.99 (m, 2H),
25 0.90-0.83 (m, 2H), 0.68-0.59 (m, 4H).

1 Benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
2 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (**Compound 48, General**
3 **Formula 1)**

4 Following general procedure L and using benzeneacetic acid, 4-[(8-
5 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
6 cyclopropane]-6-yl)ethynyl]-methyl ester (**Compound 47**, 0.96g, 0.24mmol),
7 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by
8 flash column chromatography over silica gel (230-400 mesh) using 15%
9 methanol in dichloromethane as the eluent, the title compound was obtained
10 as a solid (0.084g, 91%).

11 ¹H NMR (300 MHz, CDCl₃): δ 10.27 (br s, 1H), 7.46 (d, 2H, *J* = 8.2Hz),
12 7.30 (d, 1H, *J* = 1.8Hz), 7.23 (d, 2H, *J* = 8.2Hz), 6.80 (d, 1H, *J* = 1.5Hz),
13 3.63 (s, 2H), 2.07-1.94 (m, 1H), 1.89 (s, 2H), 1.39 (s, 6H), 1.03-0.98 (m,
14 2H), 0.89-0.82 (m, 2H), 0.73-0.59 (m, 4H).

15 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
16 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester
17 (**Compound 49, General Formula 1)**

18 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
19 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
20 (**Intermediate 44**, 0.125g, 0.5mmol), methyl-2-fluoro-4-iodo phenyl acetate
21 (**Reagent H**, 0.14g, 0.5mmol), triethyl amine (3mL), tetrahydrofuran (3mL),
22 copper(I)iodide (0.020g, 0.1mmol) and
23 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed
24 by preparative normal phase HPLC using 10% ethyl acetate in hexane as the
25 mobile phase, the title compound was obtained (0.096g, 46%).
26 ¹H NMR (300 MHz, CDCl₃): δ 7.30 (d, 1H, *J* = 2.1Hz), 7.26-7.18 (m, 3H),
27 6.80 (d, 1H, *J* = 1.8Hz), 3.71 (s, 3H), 3.67 (s, 2H), 2.04-1.94 (m, 1H), 1.90

1 (s, 2H), 1.40 (s, 6H), 1.18-0.99 (m, 2H), 0.90-0.83 (m, 2H), 0.68-0.59 (m,
2 4H).

3 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
4 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid (Compound 50,
5 **General Formula 1**)

6 Following general procedure L and using 4-[(8-cyclopropyl-3,4-
7 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
8 yl)ethynyl]-2-fluoro-benzeneacetic acid methyl ester (Compound 49,
9 0.096g, 0.23mmol), 5mL of methanol and 1M sodium hydroxide solution
10 (2mL) followed by flash column chromatography over silica gel (230-400
11 mesh) using 15% methanol in dichloromethane as the eluent, the title
12 compound was obtained as a solid (0.093g, 100%).
13 ¹H NMR (300 MHz, CDCl₃): δ 9.50 (br s, 1H), 7.27 (d, 1H, *J* = 2.1Hz), 7.24-
14 7.15 (m, 3H), 6.77 (d, 1H, *J* = 1.5Hz), 3.67 (s, 2H), 2.01-1.91 (m, 1H), 1.87
15 (s, 2H), 1.36 (s, 6H), 1.01-0.96 (m, 2H), 0.87-0.80 (m, 2H), 0.65-0.56 (m,
16 4H).

17 Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-
18 benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 51,
19 **General Formula 1**)

20 Following general procedure F and using 8-cyclopropyl-6-ethynyl-
21 3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]
22 (**Intermediate 44**, 0.05g, 0.2mmol), ethyl-4-iodo-benzoate (**Reagent A**,
23 0.055g, 0.2mmol), triethyl amine (3mL), tetrahydrofuran(3mL),
24 copper(I)iodide(0.020g, 0.1mmol) and
25 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol), the title
26 compound was obtained (0.06g, 75%).

¹H NMR (300 MHz, CDCl₃): δ 8.00 (d, 2H, *J* = 8.2Hz), 7.55 (d, 2H, *J* = 8.2Hz), 7.33 (d, 1H, *J* = 1.8Hz), 6.83 (d, 1H, *J* = 2.1Hz), 4.38 (q, 2H, *J* = 7.1Hz), 2.04-1.95 (m, 1H), 1.91 (s, 2H), 1.40 (s, 6H), 1.40 (t, 3H, *J* = 7.0Hz), 1.05-0.95 (m, 2H), 0.91-0.84 (m, 2H), 0.69-0.61 (m, 4H).

Benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 52, General Formula 1)

Following general procedure L and using benzoic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (Compound 51, 0.06g, 0.15mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL) followed by preparative reverse phase HPLC using 10% water in acetonitrile as the mobile phase, the title compound was obtained as a solid (0.040g, 72%).

¹H NMR (300 MHz, CDCl₃): δ 8.08 (d, 2H, *J* = 8.8Hz), 7.60 (d, 2H, *J* = 8.8Hz), 7.34 (d, 1H, *J* = 1.9Hz), 6.84 (d, 1H, *J* = 1.9Hz), 2.05-1.96 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.05-0.95 (m, 2H), 0.92-0.83 (m, 2H), 0.75-0.60 (m, 4H).

4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid methyl ester (Compound 53, General Formula 1)

Following general procedure F and using 8-cyclopropyl-6-ethynyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane] (Intermediate 44, 0.03g, 0.11mmol), methyl-2-fluoro-4-iodo-benzoate (Reagent G, 0.025g, 0.09mmol), triethyl amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.020g, 0.1mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed by preparative normal phase HPLC using 10% ethyl acetate in hexane as the

1 mobile phase, the title compound was obtained as a white solid (0.019g,
2 40%).

3 ¹H NMR (300 MHz, CDCl₃): δ 7.97 (t, 1H, *J* = 7.8Hz), 7.34 (d, 1H, *J* =
4 1.9Hz), 7.32-7.25 (m, 2H), 6.83 (d, 1H, *J* = 1.9Hz), 3.95 (s, 3H), 2.06-1.96
5 (m, 1H), 1.93 (s, 2H), 1.42 (s, 6H), 1.06-1.02 (m, 2H), 0.91-0.86 (m, 2H),
6 0.71-0.61 (m, 4H).

7 4-[(8-Cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-
8 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzoic acid (Compound 54,
9 **General Formula 1)**

10 Following general procedure L and using 4-[(8-cyclopropyl-3,4-
11 dihydro-4,4-dimethylspiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
12 yl)ethynyl]-2-fluoro-benzoic acid methyl ester (**Compound 53**, 0.019g,
13 0.047mmol), 5mL of methanol and 1M sodium hydroxide solution (2mL)
14 followed by preparative reverse phase HPLC using 10% water in acetonitrile
15 as the mobile phase, the title compound was obtained as a solid (0.01g,
16 56%).

17 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (t, 1H, *J* = 8.0Hz), 7.36 -7.28 (m, 3H),
18 6.83 (d, 1H, *J* = 1.9Hz), 2.18-1.95 (m, 1H), 1.92 (s, 2H), 1.41 (s, 6H), 1.06-
19 1.01 (m, 2H), 0.96-0.83 (m, 2H), 0.76-0.60 (m, 4H).

20 8-Acetyl-6-bromo-2,2,4,4-tetramethyl chroman (Intermediate 45)

21 A stirred, cooled (ice bath) suspension of aluminum chloride (0.99g,
22 7.46mmol) in anhydrous dichloromethane (20 mL) was treated with acetyl
23 chloride (0.58g, 7.46mmol). After 5 minutes, a solution of 6-bromo-2,2,4,4-
24 tetramethyl chroman (1g, 3.73mmol) in dichloromethane was added. The
25 reaction was allowed to warm to ambient temperature and stirred for 2h.
26 The reaction mixture was then poured into ice containing 10% hydrochloric
27 acid and extracted with diethyl ether (x2). The combined organic phase was
28 washed with saturated aqueous sodium bicarbonate solution, dried over

1 anhydrous sodium sulfate, filtered and evaporated in *vacuo* to a residue
2 which was subjected to flash column chromatography over silica gel (230-
3 400 mesh) using 5% ethyl acetate in hexane as the eluent to afford the title
4 compound as a pale yellow oil (0.95g, 83%). It was used as such for the next
5 step without any characterization.

6 6-Bromo-8-ethyl-2,2,4,4-tetramethyl chroman (**Intermediate 46**)

7 A stirred, cooled (ice bath) solution of 8-acetyl-6-bromo-2,2,4,4-
8 tetramethyl chroman (**Intermediate 45**, 0.95g, 3.1mmol) in trifluoroacetic
9 acid (10mL) was treated with triethylsilane (10mL) and the resulting reaction
10 mixture was allowed to warm to ambient temperature and stirred overnight.
11 The volatiles were distilled off in *vacuo* and the residue was diluted with
12 water and extracted with hexane (x2). The combined organic phase was
13 dried over anhydrous sodium sulfate, filtered and evaporated in *vacuo* to an
14 oil which was subjected to flash column chromatography over silica gel
15 (230-400 mesh) using hexane as the eluent to afford the title compound as a
16 clear oil, contaminated with a small amount to triethylsilane (0.51g, 56%).
17 ¹H NMR (300 MHz, CDCl₃): δ 7.23 (d, 1H, *J* = 2.3Hz), 7.08 (d, 1H, *J* =
18 2.3Hz), 2.58 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H), 1.17
19 (t, 3H, *J* = 7.6Hz).

20 8-Ethyl-6-trimethylsilyl-ethynyl-2,2,4,4-tetramethyl chroman
21 (**Intermediate 47**)

22 Following general procedure D and using 6-bromo-8-ethyl-2,2,4,4-
23 tetramethyl chroman (**Intermediate 46**, 0.5g, 1.61mmol),
24 (trimethylsilyl)acetylene (1.57g, 16.1mmol), triethyl amine (8mL), anhydrous
25 tetrahydrofuran (10mL), copper(I)iodide (0.025g, 0.13mmol) and
26 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol), followed
27 by flash column chromatography over silica gel (230-400 mesh) using 5%

1 ethyl acetate in hexane as the eluent, the title compound was obtained as an
2 oil (0.137g, 27%).

3 ¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, 1H, *J* = 2.1Hz), 7.10 (d, 1H, *J* =
4 2.1Hz), 2.55 (q, 2H, *J* = 7.6Hz), 1.81 (s, 2H), 1.33 (s, 6H), 1.32 (s, 6H), 1.15
5 (t, 3H, *J* = 7.6Hz), 0.24 (s, 9H).

6 8-Ethyl-6-ethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 48**)

7 Following general procedure E and using 8-ethyl-6-
8 trimethylsilanylethynyl-2,2,4,4-tetramethyl chroman (**Intermediate 47**,
9 0.137g, 0.44mmol), methanol and potassium carbonate (0.1g, 0.72mmol)
10 followed by flash column chromatography over silica gel (230-400 mesh)
11 using 5% ethyl acetate in hexane as the eluent, the title compound was
12 obtained as an oil (0.066g, 62%).

13 ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, 1H, *J* = 2.2Hz), 7.15 (d, 1H, *J* =
14 1.6Hz), 2.99 (s, 1H), 2.59 (q, 2H, *J* = 7.6Hz), 1.84 (s, 2H), 1.37 (s, 6H), 1.35
15 (s, 6H), 1.19 (t, 3H, *J* = 7.6Hz).

16 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid
17 methyl ester (**Compound 55, General Formula 8**)

18 Following general procedure F and using 8-ethyl-6-ethynyl-2,2,4,4-
19 tetramethylchroman (**Intermediate 48**, 0.033g, 0.136mmol), methyl-4-iodo
20 phenyl acetate (**Reagent B**, 0.034g, 0.12mmol), triethyl amine (2mL),
21 tetrahydrofuran (2mL), copper(I)iodide (0.025g, 0.13mmol) and
22 dichlorobis(triphenylphosphine)palladium(II) (0.075g, 0.11mmol) the title
23 compound was obtained (0.035g, 73%).

24 ¹H NMR (300 MHz, CDCl₃): δ 7.49 (d, 2H, *J* = 7.9Hz), 7.35 (d, 1H, *J* =
25 1.8Hz), 7.26 (d, 2H, *J* = 7.9Hz), 7.18 (d, 1H, *J* = 1.9Hz), 3.72 (s, 3H), 3.65
26 (s, 2H), 2.61 (q, 2H, *J* = 7.5Hz), 1.85 (s, 2H), 1.38 (s, 12H), 1.21 (t, 3H, *J* =
27 7.5Hz).

1 [4-(8-Ethyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl) phenyl] acetic acid

2 **(Compound 56, General Formula 8)**

3 Following general procedure L and using [4-(8-ethyl-2,2,4,4-
4 tetramethyl-chroman-6-ylethynyl) phenyl] acetic acid methyl ester
5 **(Compound 55, 0.035g, 0.1mmol)**, 5mL of methanol and 1M sodium
6 hydroxide solution (1mL) followed by preparative reverse phase HPLC
7 using 10% water in acetonitrile as the mobile phase, the title compound was
8 obtained as a solid (0.11g, 25%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, 2H, *J* = 8.0Hz), 7.33 (d, 1H, *J* =
10 1.9Hz), 7.25 (d, 2H, *J* = 8.0Hz), 7.15 (d, 1H, *J* = 1.9Hz), 3.65 (s, 2H), 2.59
11 (q, 2H, *J* = 7.5Hz), 1.83 (s, 2H), 1.35 (s, 12H), 1.18 (t, 3H, *J* = 7.4Hz).

12 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-
13 cyclopropyl-3,4-dihydro-4,4-dimethyl- **(Intermediate 49)**

14 Following general procedure R and using 6-bromo-8-cyclopropyl-3,4-
15 dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]
16 **(Intermediate 42, 0.45g, 1.48mmol)**, anhydrous tetrahydrofuran (5mL),
17 1.7M solution of *tert*-butyl lithium solution in pentane (1.74mL, 2.96mmol)
18 and carbon dioxide generated from dry ice, followed by flash column
19 chromatography over silica gel (230-400 mesh) using 50% ethyl acetate in
20 hexane as the eluent, the title compound was obtained as a white solid
21 (0.34g, 85%).

22 ¹H NMR (300 MHz, CDCl₃): δ 12.43 (br s, 1H), 7.94 (d, 1H, *J* = 2.1Hz),
23 7.42 (d, 1H, *J* = 1.8Hz), 2.06-1.96 (m, 1H), 1.92 (s, 2H), 1.42 (s, 6H), 1.12-
24 0.97 (m, 2H), 0.95-0.81 (m, 2H), 0.77-0.60 (m, 4H).

25 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-
26 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-butoxycarbonylmethyl)phenyl
27 ester **(Compound 57, General Formula 1)**

1 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-
2 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (**Intermediate 49**,
3 0.06g, 0.22mmol) in anhydrous dichloromethane (5mL) was treated with
4 *tert*-butyl-4-hydroxy phenyl acetate (**Reagent E**, 0.05g, 0.22mmol) followed
5 by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11g,
6 0.22mmol) and 4-dimethylaminopyridine (0.028g, 0.22mmol). The resulting
7 solution was stirred at ambient temperature overnight. The reaction mixture
8 was subjected to flash column chromatography over silica gel (230-400
9 mesh) using 7% ethyl acetate in hexane as the eluent to afford the title
10 compound as a clear oil that solidified on standing (0.048g, 48%).
11 ¹H NMR (300 MHz, CDCl₃): δ 7.91 (d, 1H, *J* = 2.1Hz), 7.41 (d, 1H, *J* =
12 1.8Hz), 7.24 (d, 2H, *J* = 8.8Hz), 7.05 (d, 2H, *J* = 8.5Hz), 3.46 (s, 2H), 1.97-
13 1.90 (m, 1H), 1.87 (s, 2H), 1.37 (s, 9H), 1.36 (s, 6H), 1.04-0.90 (m, 2H),
14 0.87-0.75 (m, 2H), 0.65-0.56 (m, 4H).
15 Spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-
16 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester
17 (**Compound 58**, **General Formula 1**)

18 A solution of spiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-
19 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 4-(*tert*-
20 butoxycarbonylmethyl)phenyl ester (**Compound 57**, 0.048g, 0.105mmol)
21 was treated with 2mL of trifluoroacetic acid and stirred at ambient
22 temperature for 2h. The trifluoroacetic acid was distilled off under reduced
23 pressure and the residue was subjected to preparative reverse phase HPLC
24 using 10% water in acetonitrile as the mobile phase to afford the title
25 compound as a white solid (0.029g, 55%).
26 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (d, 1H, *J* = 2.2Hz), 7.48 (d, 1H, *J* =
27 1.9Hz), 7.34 (d, 2H, *J* = 8.5Hz), 7.16 (d, 2H, *J* = 8.5Hz), 3.67 (s, 2H), 2.07-

1 1.97 (m, 1H), 1.95 (s, 2H), 1.44 (s, 6H), 1.09-1.04 (m, 2H), 0.93-0.85 (m,
2 2H), 0.79-0.64 (m, 4H).
3 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-
4 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(tert-butoxycarbonylmethyl)phenyl
5 ester (Compound 59, General Formula 1)

6 A solution of spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
7 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl- (Intermediate 49,
8 0.05g, 0.18mmol) in anhydrous dichloromethane (5mL) was treated with
9 tert-butyl-3-hydroxy phenyl acetate (Reagent F, 0.04g, 0.18mmol) followed
10 by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.029g,
11 0.1mmol) and 4-dimethylaminopyridine (0.022g, 0.18mmol). The resulting
12 solution was stirred at ambient temperature overnight. The reaction mixture
13 was subjected to flash column chromatography over silica gel (230-400
14 mesh) using 7% ethyl acetate in hexane as the eluent to afford the title
15 compound as a clear oil that solidified on standing (0.020g, 23%).
16 ¹H NMR (300 MHz, CDCl₃): δ 7.98 (d, 1H, *J* = 1.9Hz), 7.48 (d, 1H, *J* =
17 2.2Hz), 7.38 (t, 1H, *J* = 7.7Hz), 7.19-7.11 (m, 3H), 3.68 (s, 2H), 2.05-1.94
18 (m, 1H), 1.95 (s, 2H), 1.44 (s, 15H), 1.09-1.04 (m, 2H), 0.96-0.82 (m, 2H),
19 0.73-0.64 (m, 4H).

20 Spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-
21 cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester
22 (Compound 60, General Formula 1)

23 A solution of spiro[2H-1-benzopyran-2,1'-cyclopropane]-6-
24 carboxylic acid, 8-cyclopropyl-3,4-dihydro-4,4-dimethyl-, 3-(tert-
25 butoxycarbonylmethyl)phenyl ester (Compound 59, 0.020g, 0.04mmol) was
26 treated with 2mL of trifluoroacetic acid and stirred at ambient temperature
27 for 2h. The trifluoroacetic acid was distilled off under reduced pressure and
28 the residue was subjected to preparative reverse phase HPLC using 10%

1 water in acetonitrile as the mobile phase to afford the title compound as a
2 white solid (0.0125g, 62%).

3 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (d, 1H, *J* = 2.1Hz), 7.49 (d, 1H, *J* =
4 2.1Hz), 7.36 (t, 1H, *J* = 7.8Hz), 7.18-7.08 (m, 3H), 3.56 (s, 2H), 2.06-1.95
5 (m, 1H), 1.95 (s, 2H), 1.45 (s, 6H), 1.09-1.05 (m, 2H), 0.96-0.84 (m, 2H),
6 0.74-0.65 (m, 4H).

7 6-Bromo-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-1-carbaldehyde
8 **(Intermediate 50)**

9 A solution of 6-bromo-4,4-dimethyl-1,2,3,4-tetrahydroquinoline,
10 available in accordance with United States Patent No. 5,089,509, the
11 specification of which is incorporated herein by reference (1.8g, 7.5mmol) in
12 10mL of formic acid was refluxed for 3h. The reaction mixture was then
13 cooled to ambient temperature and poured into ice-cold saturated aqueous
14 sodium bicarbonate solution and extracted with diethyl ether (x2). The
15 combined organic phase was dried over anhydrous sodium sulfate, filtered
16 and evaporated in *vacuo* to a residue which was subjected to flash column
17 chromatography over silica gel (230-400 mesh) using 15-25% ethyl acetate
18 in hexane as the eluent to afford the title compound as a pale yellow solid
19 (1.8g, 90%).

20 ¹H NMR (300 MHz, CDCl₃): δ 8.71 (s, 1H), 7.45 (d, 1H, *J* = 2.2Hz), 7.28
21 (dd, 1H, *J* = 2.2, 8.5Hz), 6.98 (d, 1H, *J* = 8.5Hz), 3.78 (t, 2H, *J* = 6.3Hz),
22 1.74 (t, 2H, *J* = 6.3Hz), 1.28 (s, 6H).

23 6-Bromo-1-cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline
24 **(Intermediate 51)**

25 A stirred, cooled (0°C) solution of 6-bromo-4,4-dimethyl-1,2,3,4-
26 tetrahydro-quinoline-1-carbaldehyde (**Intermediate 50**, 21.8, 6.7mmol) in
27 anhydrous tetrahydrofuran (20mL) under argon was treated with titanium
28 tetra-*iso*-propoxide (2.15mL, 7.39mmol) followed by 3M solution of ethyl

1 magnesium bromide in diethyl ether (5.6mL, 16.8mmol) and the reaction
2 mixture was then heated at 50°C overnight. It was then cooled in an ice-
3 bath, quenched with saturated aqueous ammonium chloride solution and
4 extracted with diethyl ether (x2). The combined organic phase was dried
5 over anhydrous sodium sulfate, filtered over celite and evaporated in *vacuo*
6 to residue which was subjected to flash column chromatography over silica
7 gel (230-400 mesh) using 5% ethyl acetate in hexane as the eluent to afford
8 the title compound as an oil (1.2g, 64%).

9 ¹H NMR (300 MHz, CDCl₃): δ 7.24 (d, 1H, *J* = 2.5Hz), 7.12 (dd, 1H, *J* =
10 2.2, 8.8Hz), 7.01 (d, 1H, *J* = 8.8Hz), 3.20 (t, 2H, *J* = 6.0Hz), 2.27-2.20 (m,
11 1H), 1.68 (t, 2H, *J* = 5.9Hz), 1.24 (s, 3H), 1.23 (s, 3H), 0.83-0.77 (m, 2H),
12 0.60-0.55 (m, 2H).

13 1-Cyclopropyl-6-trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydro-
14 quinoline (Intermediate 52)

15 Following general procedure D and using 6-bromo-1-cyclopropyl-4,4-
16 dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 51, 0.8g, 2.86mmol),
17 (trimethylsilyl)acetylene (5mL, 35mmol), triethyl amine (10mL), anhydrous
18 tetrahydrofuran, copper(I)iodide (0.080g, 0.42mmol) and
19 dichlorobis(triphenylphosphine)palladium(II) (0.240g, 0.34mmol), the title
20 compound was obtained as an oil (0.67g, 79%).

21 ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, 1H, *J* = 1.8Hz), 7.22 (dd, 1H, *J* =
22 2.1, 8.5Hz), 7.06 (d, 1H, *J* = 8.5Hz), 3.27 (t, 2H, *J* = 5.9Hz), 2.37-2.31 (m,
23 1H), 1.70 (t, 2H, *J* = 6.0Hz), 1.28 (s, 6H), 0.89-0.82 (m, 2H), 0.66-0.60 (m,
24 2H), 0.28 (s, 9H).

25 1-Cyclopropyl-6-ethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline:
26 (Intermediate 53)

27 Following general procedure E and using 1-cyclopropyl-6-
28 trimethylsilanylethynyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

1 (Intermediate 52, 0.40g, 1.34mmol), methanol and potassium carbonate
2 (0.2g, 1.47mmol) followed by flash column chromatography over silica gel
3 (230-400 mesh) using 2% ethyl acetate in hexane as the eluent, the title
4 compound was obtained as an oil (0.17g, 56%).

5 ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, 1H, *J* = 2.1Hz), 7.27 (dd, 1H, *J* =
6 2.1, 8.5Hz), 7.11 (d, 1H, *J* = 8.5Hz), 3.30 (t, 2H, *J* = 6.0Hz), 3.02 (s, 1H),
7 2.40-2.34 (m, 1H), 1.74 (t, 2H, *J* = 6.0Hz), 1.30 (s, 6H), 0.93-0.85 (m, 2H),
8 0.70-0.63 (m, 2H).

9 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-
10 benzoic acid ethyl ester (Compound 61, General Formula 7)

11 Following general procedure F and using 1-cyclopropyl-6-ethynyl-
12 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 53, 0.11g,
13 0.43mmol), ethyl-4-iodo-benzoate (Reagent A, 0.11g, 0.9mmol), triethyl
14 amine (3mL), tetrahydrofuran(3mL), copper(I)iodide(0.02g, 0.1mmol) and
15 dichlorobis(triphenylphosphine)palladium(II) (0.060g, 0.085mmol) followed
16 by flash column chromatography over silica gel (230-400 mesh) using 5-
17 10% ethyl acetate in hexane as the eluent, the title compound was obtained
18 (0.05g, 31%).

19 ¹H NMR (300 MHz, CDCl₃): δ 7.99 (d, 2H, *J* = 8.2Hz), 7.54 (d, 2H, *J* =
20 8.2Hz), 7.37 (d, 1H, *J* = 2.1Hz), 7.26 (dd, 1H, *J* = 2.1, 8.5Hz), 7.10 (d, 1H, *J* =
21 8.8Hz), 4.37 (q, 2H, *J* = 7.1Hz), 3.28 (t, 2H, *J* = 6.0Hz), 2.40-2.33 (m,
22 1H), 1.71 (t, 2H, *J* = 5.8Hz), 1.40 (t, 3H, *J* = 7.0Hz), 1.27 (s, 6H), 0.94-0.82
23 (m, 2H), 0.65-0.60 (m, 2H).

24 4-(1-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-
25 benzoic acid (Compound 62, General Formula 7)

26 Following general procedure L and using 4-(1-cyclopropyl-4,4-
27 dimethyl-1,2,3,4-tetrahydro-quinolin-6-ylethynyl)-benzoic acid ethyl ester

1 (Compound 61, 0.05g, 0.13mmol), 5mL of ethanol and 5M sodium
2 hydroxide solution (2mL) followed by recrystallization from hot ethyl
3 acetate, the title compound was obtained as a solid (0.030g, 64%).
4 ¹H NMR (300 MHz, DMSO-d₆): δ 7.92 (d, 2H, J = 8.2Hz), 7.57 (d, 2H, J =
5 8.2Hz), 7.33 (d, 1H, J = 1.9Hz), 7.23 (dd, 1H, J = 1.9, 8.5Hz), 7.06 (d, 1H, J
6 = 8.8Hz), 3.25 (t, 2H, J = 5.8Hz), 2.41-2.34 (m, 1H), 1.64 (t, 2H, J = 5.6Hz),
7 1.21 (s, 6H), 0.87-0.81 (m, 2H), 0.59-0.54 (m, 2H).

8 [4-(1-Cyclopropyl)-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-
9 ethynyl]phenyl] acetic acid methyl ester (Compound 63, General Formula
10 7)

11 Following general procedure F and using 1-cyclopropyl-6-ethynyl-
12 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 53, 0.05g,
13 0.22mmol), methyl-4-iodo-phenyl acetate (Reagent B, 0.055g, 0.2mmol),
14 triethyl amine (5mL), tetrahydrofuran, copper(I)iodide(0.025g, 0.13mmol)
15 and dichlorobis(triphenylphosphine)palladium(II) (0.75g, 0.11mmol)
16 followed preparative normal phase HPLC using 10 % ethyl acetate in hexane
17 as the mobile phase, the title compound was obtained (0.089g, 100%).
18 ¹H NMR (300 MHz, CDCl₃): δ 7.47 (d, 2H, J = 8.8Hz), 7.45 (d, 1H, J =
19 1.8Hz), 7.35-7.22 (m, 2H), 7.10 (d, 2H, J = 8.8Hz), 3.70 (s, 3H), 3.63 (s,
20 2H), 3.27 (t, 2H, J = 6.0Hz), 2.37-2.31 (m, 1H), 1.71 (t, 2H, J = 6.0Hz), 1.27
21 (s, 6H), 0.89-0.81 (m, 2H), 0.65-0.60 (m, 2H).

22 [4-(1-Cyclopropyl)-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)-2-
23 fluoro-phenyl] acetic acid ethyl ester (Compound 64, General Formula 7)

24 Following general procedure F and using 1-cyclopropyl-6-ethynyl-
25 4,4-dimethyl-1,2,3,4-tetrahydro quinoline (Intermediate 53, 0.11g,
26 0.49mmol), ethyl-2-fluoro-4-iodo-phenyl acetate (Reagent C, 0.11g,
27 0.9mmol), triethyl amine (3mL), tetrahydrofuran(3mL),

1 copper(I)iodide(0.06g, 0.32mmol) and
2 dichlorobis(triphenylphosphine)palladium(II) (0.25g, 0.36mmol) followed by
3 flash column chromatography over silica gel (230-400 mesh) using 10 %
4 ethyl acetate in hexane as the eluent, the title compound was obtained (0.1g,
5 51%). ¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, 1H, *J* = 2.1Hz), 7.25-7.17 (m,
6 3H), 7.09 (d, 2H, *J* = 8.8Hz), 4.17 (q, 2H, *J* = 7.1Hz), 3.65 (s, 2H), 3.27 (t,
7 2H, *J* = 6.0Hz), 2.38-2.31 (m, 1H), 1.69 (t, 2H, *J* = 6.0Hz), 1.27 (s, 6H), 1.25
8 (t, 3H, *J* = 7.1Hz), 0.88-0.81 (m, 2H), 0.65-0.59 (m, 2H).

9 N-(4-Bromophenyl)-N-methyl-3-methyl-2-butenamide (Intermediate 54)

10 3,3-Dimethylacryloyl chloride (3mL, 27mmol) was added to a
11 solution of 4-bromo-N-methyl-aniline (4.55g, 25mmol) in 150mL of
12 dichloromethane followed after 5 minutes by triethyl amine (5mL, 33mmol).
13 After 2.5h at ambient temperature, the reaction mixture was washed with
14 water and the organic phase was dried over anhydrous sodium sulfate and
15 evaporated in vacuo to afford the title product as a brown oil in quantitative
16 yield.

17 ¹H-NMR (300 MHz, CDCl₃): d 1.71 (s, 3H), 2.11(s, 3H), 3.28(s, 3H), 5.47(s,
18 1H), 7.05(d, *J* = 8.5Hz, 2H), 7.50(d, *J* = 8.2Hz, 2H).

19 6-Bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (Intermediate
20 55)

21 N-(4-bromophenyl)-N-methyl-3-methyl-2-butenamide
22 (Intermediate 54, 6.42g, 24mmol) was heated to 130°C and aluminum
23 chloride (5g, 37.4mmol) was added in portions over 0.5h. The reaction
24 mixture was stirred for 1 hour at the same temperature and then cooled to
25 room temperature. Ice was added cautiously to the solid, followed by
26 ~200mL of iced water. The reaction mixture was then extracted with ether
27 (x2) and dichloromethane (x1) and the combined organic phase was dried
28 over anhydrous magnesium sulfate and evaporated in *vacuo* to yield a brown

1 solid. The solid was treated with hexane-dichloromethane and filtered to
2 afford 1.7g of product. The mother liquor was evaporated and purified by
3 flash column chromatography on silica gel (230-400 mesh) to afford 2.9g of
4 the title compound as a solid (total 72%).

5 ¹H-NMR (300 MHz, CDCl₃): δ 1.29(s, 6H), 2.49(s, 2H), 3.36(s, 3H), 6.87(d,
6 *J* = 8.2Hz, 1H), 7.36(dd, *J* = 2.0, 8.5Hz, 1H), 7.39(d, *J* = 2.0Hz, 1H).

7 6-Bromo-1,4,4-trimethylspiro[2H-1-1,2,3,4-tetrahydroquinoline-2,1'-
8 cyclopropane] (Intermediate 56)

9 A stirred, cooled (-78°C) 3M solution of ethyl magnesium bromide in
10 ether (8.1mL, 24.25mmol) under argon was treated with anhydrous
11 tetrahydrofuran (20mL) followed by a solution of titanium tetra-*iso*-
12 propoxide (3.15mL, 10.2mmol) in tetrahydrofuran (10mL). A solution of 6-
13 bromo-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline (Intermediate 55,
14 2.6g, 9.7mmol) was cannulated into the reaction mixture and the solution
15 was allowed to warm to room temperature overnight. It was then cooled in
16 an ice-bath, quenched with saturated aqueous ammonium chloride solution,
17 filtered over celite and the aqueous phase was extracted with diethyl ether
18 (x2). The combined organic phase was dried over anhydrous magnesium
19 sulfate, filtered and evaporated in *vacuo* to afford an orange oil. Flash
20 column chromatography over silica gel (230-400 mesh) using 2-4% ethyl
21 acetate in hexane as the eluent afforded the title compound as an oil which
22 was ~70% pure (1.7g, 63%) and 0.5g of recovered starting material.

23 ¹H-NMR (300 MHz, CDCl₃): δ 0.58(t, *J* = 6.0Hz, 2H), 0.91(t, *J* = 6.0Hz,
24 2H), 1.35 (s, 6H), 1.70(s, 2H), 2.68 (s, 3H), 6.59 (d, *J* = 8.8Hz, 1H), 7.16(dd,
25 *J* = 2.3, 8.8Hz, 1H), 7.33(d, *J* = 2.3Hz, 1H).

26 1,4,4-Trimethyl-6-(trimethylsilyl)ethynylspiro[2H-1-1,2,3,4-
27 tetrahydroquinoline-2,1'-cyclopropane] (Intermediate 57)

1 Following general procedure D and using 6-bromo-1,4,4-
2 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]
3 (**Intermediate 56**, 0.56g, 2mmol), (trimethylsilyl)acetylene (1.13mL,
4 8mmol), triethyl amine (4mL), anhydrous tetrahydrofuran (5mL),
5 copper(I)iodide (0.08g, 0.4mmol) and
6 dichlorobis(triphenylphosphine)palladium(II) (0.28g, 0.4mmol), followed by
7 flash column chromatography over silica gel (230-400 mesh) using hexane-
8 2% ethyl acetate in hexane as the eluent, the title compound was obtained as
9 an oil (0.42g, 70%).

10 ¹H NMR (300 MHz, CDCl₃): δ 0.023(s, 9H), 0.33(t, *J* = 6.1Hz, 2H), 0.71(t, *J*
11 = 6.1Hz, 2H), 1.10(s, 6H), 1.45(s, 2H), 2.41 (s, 3H), 6.31(d, *J* = 8.5Hz, 1H),
12 6.96 (dd, *J* = 2.1, 8.5Hz, 1H), 7.10(d, *J* = 2.1Hz, 1H).

13 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-
14 2,1'-cyclopropane]-6-yl)ethynyl]-ethyl ester (**Compound 65**, **General**
15 **Formula 1**)

16 Following general procedure E and using a solution of 1,4,4-
17 trimethyl-6-(trimethylsilanyl)ethynylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-
18 2,1'-cyclopropane] (**Intermediate 57**, 0.416g, 1.4mmol), methanol (10mL),
19 ethyl acetate (2mL) and potassium carbonate (1.08g, mmol) a silyl
20 deprotected acetylenic intermediate was obtained which was used directly
21 for the next step (0.25g, 79%). Following general procedure F and using part
22 of the acetylenic intermediate obtained as above (0.11g, 0.5mmol), ethyl-4-
23 iodo benzoate (**Reagent A**, 0.112g, 0.4mmol), triethyl amine (1mL),
24 tetrahydrofuran (2.5mL), copper(I)iodide (0.050g, 0.26mmol) and
25 tetrakis(triphenylphosphine)palladium(0) (0.096g, 0.17mmol) followed by
26 flash column chromatography over silica gel (230-400 mesh) using 8% ethyl
27 acetate in hexane as the eluent and preparative HPLC on Partisil 10 silica

1 column using 10% ethyl acetate in hexane as the mobile phase, the title
2 compound was obtained as a yellow oil (0.048g, 26%).
3 ¹H-NMR (300 MHz, CDCl₃): δ 0.60 (t, *J* = 6.1Hz, 2H), 0.99(t, *J* = 6.1Hz,
4 2H), 1.37(s, 6H), 1.42(t, *J* = 7.0Hz, 3H), 1.73(s, 2H), 2.68(s, 3H), 4.40 (q, *J*
5 = 7.0Hz, 2H), 6.61(d, *J* = 8.8Hz, 1H), 7.28 (dd, *J* = 2.1, 8.5Hz, 1H), 7.42 (d,
6 *J* = 2.1Hz, 1H), 7.57(d, *J* = 8.2Hz, 2H), 8.01(d, *J* = 8.2Hz, 2H).

7 Benzoic acid, 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-
8 2,1'-cyclopropane]-6-yl)ethynyl]- (Compound 66, General Formula 1)

9 Following general procedure I and using benzoic acid, 4-[(1,4,4-
10 trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-cyclopropane]-6-
11 yl)ethynyl]-ethyl ester (Compound 65, 0.03g, 0.08mmol), ethanol (2mL),
12 tetrahydrofuran (2mL) and 1M aqueous sodium hydroxide solution (1mL),
13 the title compound was obtained as a yellow solid (0.020g, 67%).

14 ¹H-NMR (300 MHz, CD₃COCD₃): δ 0.60 (t, *J* = 5.8Hz, 2H), 1.03(t, *J* =
15 5.8Hz, 2H), 1.34(s, 6H), 1.74(s, 2H), 2.69(s, 3H), 6.60(d, *J* = 8.5Hz, 1H),
16 7.23 (dd, *J* = 2.0, 8.4Hz, 1H), 7.39 (d, *J* = 2.0Hz, 1H), 7.58(d, *J* = 8.2Hz,
17 2H), 8.01(d, *J* = 8.2Hz, 2H).

18 Esterification Methods:

19 Method A:

20 The carboxylic acid was combined with a solution of the desired
21 alcohol and concentrated sulfuric acid (20 to 1 v/v) and the resulting
22 mixture or solution (0.75 to 1.0 M) heated to reflux overnight. The solution
23 was cooled to room temperature, diluted with Et₂O, and washed with H₂O,
24 saturated aqueous NaHCO₃, and saturated aqueous NaCl before being dried
25 over MgSO₄. Concentration of the dry solution under reduced pressure
26 afforded the desired carboxylic ester of sufficient purity to be used directly
27 in the next reaction.

1 **Method B:**

2 To a solution (0.67 to 1.0M) of the carboxylic acid in acetone was
3 added 1.1 equivalents of the desired alkyl halide and 1.0 equivalents of solid
4 potassium carbonate. The resulting mixture was heated to reflux for 2h and
5 then allowed to stir at room temperature overnight. The mixture was filtered
6 and the filtrate concentrated under reduced pressure. The product was
7 isolated from the residue by column chromatography using silica gel as the
8 solid phase.

9 **Method C:**

10 A solution (1M) of the carboxylic acid in thionyl chloride was heated
11 at reflux until analysis of a reaction aliquot by IR spectroscopy showed the
12 absence of the aryl carboxylic acid carbonyl band (1705 - 1680 cm^{-1}). The
13 solution was cooled to room temperature and concentrated under reduced
14 pressure to give the crude acyl chloride.

15 The acyl chloride was dissolved in CH_2Cl_2 and the resulting solution
16 (0.5 to 0.75M) treated with 1.1 equivalents the desired alcohol and 2.0
17 equivalents of pyridine. After stirring overnight at room temperature the
18 solution was diluted with Et_2O and washed with H_2O , 10% aqueous HCl ,
19 saturated aqueous NaHCO_3 , and saturated aqueous NaCl before being dried
20 over Na_2SO_4 . Concentration of the dry solution under reduced pressure
21 followed by column chromatography afforded the desired ester.

22 **GENERAL PROCEDURE 1 (preparation of Enol ethers):**

23 A solution (0.35 M) of the aryl ester in anhydrous THF was cooled to
24 0 °C and treated with 1.0 equivalents of Tebbe's Reagent ($[\mu\text{-chloro-}\mu\text{-}$
25 methylene[bis(cyclopentadienyl)titanium]-dimethylaluminum] 0.5 M in
26 toluene). After 30 minutes the solution was warmed to room temperature
27 and stirred for 30 minutes before being carefully added to a 0.1 N NaOH
28 solution at 0 °C. This mixture was treated with hexanes and the solids

1 removed by filtration through a pad of Celite. The solids were washed with
2 hexanes and the filtrate passed through a second pad of Celite to remove any
3 newly formed solids. The organic layer was dried (Na_2SO_4) and
4 concentrated under reduced pressure. The desired enol ether was isolated
5 from the residue by column chromatography using 1-2% of Et_3N added to
6 the eluant. (note: prolonged exposure of the product to the column can
7 result in hydrolysis and formation of the corresponding methyl ketone.)

8 GENERAL PROCEDURE 2 (cyclopropanation of the enol ethers):

9 To a solution (0.3 M) of the enol ether in anhydrous Et_2O was added
10 2.0 equivalent of Et_2Zn (as a solution in hexanes) and 2.0 equivalents of
11 CH_2I_2 . The resulting solution was heated to reflux until analysis of a
12 reaction aliquot (by TLC or ^1H NMR) indicated that all of the starting enol
13 ether had been consumed. (note: Additional equal amounts of Et_2Zn and
14 CH_2I_2 can be added to drive the reaction to completion.) Upon cooling to
15 room temperature the reaction was carefully quenched by the addition of
16 saturated aqueous NH_4Cl . The resulting mixture is extracted with Et_2O and
17 the combined organic layers washed with H_2O and saturated aqueous NaCl
18 before being dried over Na_2SO_4 and concentrated under reduced pressure.
19 The product is isolated from the residue by column chromatography.

20 1-Bromo-4-(1-methoxyvinyl)-benzene: (Intermediate 58)

21 Using General Procedure 1; methyl 4-bromo-benzoate (600.0 mg,
22 2.78 mmols), and 5.6 mL of Tebbe's Reagent (794.0 mg, 2.78 mmols)
23 afforded 420.0 mg (70%) of the title compound as a colorless oil after
24 column chromatography (100% hexanes).
25 ^1H NMR (CDCl_3) δ : 7.48 - 7.45 (4H, m), 4.64 (1H, d, $J = 2.9$ Hz), 4.23 (1H,
26 d, $J = 2.9$ Hz), 3.73 (3H, s).

27 1-Bromo-4-(1-methoxycyclopropyl)-benzene (Intermediate 59)

28 Using General Procedure 2; 1-bromo-4-(1-methoxyvinyl)-benzene

1 (Intermediate 58, 410.0 mg, 1.92 mmols), Et₂Zn (711.3 mg, 5.76 mmols),
2 and CH₂I₂ (1.54 g, 5.76 mmols) in 4.0 mL Et₂O afforded 300.0 mg (69%) of
3 the title compound as a colorless oil after chromatography (0-3% EtOAc -
4 hexanes).

5 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.5 Hz), 7.18 (2H, d, J = 8.5 Hz), 3.21
6 (3H, s), 1.19 (2H, m), 0.94 (2H, m).

7 [4-(1-Methoxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate
8 60)

9 Using General Procedure D; 1-bromo-4-(1-methoxycyclopropyl)-
10 benzene (Intermediate 59, 300.0 mg, 1.32 mmol) in triethylamine (4 mL)
11 and anhydrous tetrahydrofuran (4 mL) was treated with copper(I)iodide
12 (93.0 mg, 0.13 mmol) and then sparged with argon for 5 minutes.
13 Trimethylsilyl acetylene (1.39 g, 14.2 mmols) was then added followed by
14 dichlorobis(triphenylphosphine)palladium(II) (93.0 mg, 0.13 mmol). The
15 resulting reaction mixture was heated to 70 °C for 60h. The title compound
16 (286.0 mg, 90%) was isolated by chromatography (0 - 3% EtOAc -
17 hexanes).

18 ¹H NMR (CDCl₃) δ: 7.35 (2H, d, J = 7.2 Hz), 7.14 (2H, d, J = 7.2 Hz), 3.14
19 (3H, s), 1.14 (2H, m), 0.88 (2H, m), 0.17 (9H, s).

20 1-Ethynyl-4-(1-methoxycyclopropyl)-benzene (Intermediate 61)

21 Using General Procedure E; [4-(1-methoxycyclopropyl)-
22 phenylethynyl]-trimethylsilane (Intermediate 60, 285.0 mg, 1.18 mmols) in
23 methanol (10mL) was treated with potassium carbonate (100.0 mg, 0.72
24 mmol) and stirred overnight at ambient temperature. The crude alkyne (220
25 mg, 100%) was used directly in the next reaction.

26 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.2 Hz), 7.24 (2H, d, J = 8.2 Hz), 3.23
27 (3H, s), 3.06 (1H, s), 1.22 (2H, m), 0.98 (2H, m).

1 Ethyl 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-benzoate (Compound
2 **67, General Formula 2)**

3 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-
4 benzene (**Intermediate 61**, 100.0 mg, 0.47 mmol) and ethyl-4-iodo
5 benzoate (**Reagent A**, 141.0 mg, 0.51 mmol) in triethyl amine (6 mL) was
6 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon
7 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (109 mg, 0.16
8 mmol) was added and the reaction mixture was stirred overnight at room
9 temperature. Column chromatography (2-5% EtOAc - hexanes) afforded
10 135.0 mg (90%) of the title compound as an orange solid.

11 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.52
12 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.25
13 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.23 (2H, m), 1.00 (2H, m).

14 Methyl {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate
15 (**Compound 68, General Formula 2)**

16 Using General Procedure F; 1-ethynyl-4-(1-methoxycyclopropyl)-
17 benzene (**Intermediate 61**, 120.0 mg, 0.56 mmol) and methyl-(4-
18 iodophenyl)-acetate (**Reagent B**, 154.0 mg, 0.56 mmol) in triethyl amine (6
19 mL) was treated with copper(I)iodide (35.0 mg, 0.19 mmol) and sparged
20 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
21 (130 mg, 0.19 mmol) was added and the reaction mixture was stirred
22 overnight at room temperature. Column chromatography (2-8% EtOAc -
23 hexanes) afforded 140.0 mg (78%) of the title compound as an orange solid.

24 ¹H NMR (CDCl₃) δ: 7.50 (4H, d, J = 8.1 Hz), 7.28 (4H, d, J = 8.1 Hz), 3.76
25 (3H, s), 3.64 (2H, s), 3.25 (3H, s), 1.22 (2H, m), 0.99 (2H, m).

26 4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-benzoic acid (Compound 69,
27 **General Formula 2)**

1 Using General Procedure I; a solution of ethyl 4-[4-(1-
2 methoxycyclopropyl)-phenylethynyl]-benzoate (**Compound 67**, 110.0 mg,
3 0.34 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
4 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred
5 overnight at room temperature. Work-up afforded 85.0 mg (86%) of the
6 title compound as an orange solid.

7 ¹H NMR (CDCl₃) δ: 8.05 (2H), 7.66 (2H), 7.56 (2H, d, J = 8.5 Hz), 7.35
8 (2H, d, J = 8.6 Hz), 3.22 (3H, s), 1.21 (2H, m), 1.01 (2H, m).

9 4-[4-(1-Methoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid

10 (**Compound 70, General Formula 2**)

11 Using General Procedure I; a solution of methyl {4-[4-(1-
12 methoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 68**,
13 100.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
14 treated with NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution)
15 and stirred overnight at room temperature. Work-up afforded 80.0 mg
16 (84%) of the title compound as an orange solid.

17 ¹H NMR (CDCl₃) δ: 7.49 (4H), 7.27 (4H), 3.66 (2H, s), 3.25 (3H, s), 1.22
18 (2H, m), 0.99 (2H, m).

19 Isopropyl 4-bromobenzoate (**Intermediate 62**)

20 Using General Esterification Procedure A; 4-bromobenzoic acid
21 (1.50 g, 7.46 mmols) was combined with isopropyl alcohol to give 1.76 g
22 (97%) of the title compound as a colorless oil.

23 ¹H NMR (CDCl₃) δ: 7.90 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5
24 Hz), 5.24 (1H, septet, J = 6.2 Hz), 1.37 (6H, d, J = 6.2 Hz).

25 1-Bromo-4-(1-isopropoxyvinyl)-benzene (**Intermediate 63**)

26 Using General Procedure 1; isopropyl 4-bromobenzoate
27 (**Intermediate 62**, 780.0 mg, 3.20 mmols) and 6.4 mL of Tebbe's Reagent

1 (910.7 mg, 3.20 mmols) afforded 328.0 mg (43%) of the title compound as a
2 colorless oil after column chromatography (100% hexanes).

3 ¹H NMR (CDCl₃) δ: 7.46 (4H, m), 4.66 (1H, d, J = 2.6 Hz), 4.40 (1H, septet,
4 J = 6.2 Hz), 4.21 (1H, d, J = 2.6 Hz), 1.34 (6H, d, J = 6.2 Hz).

5 1-Bromo-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 64)

6 Using General Procedure 2; 1-bromo-4-(1-isopropoxyvinyl)-benzene
7 (Intermediate 63, 328.0 mg, 1.36 mmols), Et₂Zn (335.9 mg, 2.72 mmols),
8 and CH₂I₂ (728.0 mg, 2.72 mmols) in 4.0 mL Et₂O afforded 240.0 mg (70%)
9 of the title compound as a colorless oil after chromatography (3% EtOAc -
10 hexanes).

11 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.5 Hz), 7.27 (2H, d, J = 8.5 Hz), 3.70
12 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.06 (6H, d, J = 6.2 Hz), 0.91 (2H,
13 m).

14 [4-(1-Isopropoxycyclopropyl)-phenylethynyl]-trimethylsilane

15 (Intermediate 65)

16 Using General Procedure D; 1-bromo-4-(1-isopropoxycyclopropyl)-
17 benzene (Intermediate 64, 240.0 mg, 0.94 mmol) in triethylamine (8 mL)
18 was treated with copper(I)iodide (18.0 mg, 0.094 mmol) and then sparged
19 with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1 mmols) was
20 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (66.0
21 mg, 0.094 mmol). The resulting reaction mixture was heated to 70 °C for 5
22 days. The title compound (250.0 mg, 98%) was isolated by chromatography
23 (0 - 3% EtOAc - hexanes) as an orange oil.

24 ¹H NMR (CDCl₃) δ: 7.41 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 3.70
25 (1H, septet, J = 6.2 Hz), 1.18 (2H, m), 1.05 (6H, d, J = 6.2 Hz), 0.93 (2H,
26 m), 0.94 (9H, s).

27 1-Ethynyl-4-(1-isopropoxycyclopropyl)-benzene (Intermediate 66)

1 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-
2 phenylethynyl]-trimethylsilane (**Intermediate 65**, 260.0 mg, 0.96 mmol) in
3 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
4 mmol) and stirred overnight at ambient temperature. The crude alkyne (220
5 mg, 100%) was used directly in the next reaction.

6 ¹H NMR (CDCl₃) δ: 7.45 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz), 3.72
7 (1H, septet, J = 6.2 Hz), 3.06 (1H, s), 1.20 (2H, m), 1.07 (6H, d, J = 6.2 Hz),
8 0.95 (2H, m).

9 Ethyl 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoate

10 (**Compound 71**, General Formula 2)

11 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-
12 benzene (**Intermediate 66**, 114.0 mg, 0.57 mmol) and ethyl-4-iodo
13 benzoate (**Reagent A**, 731.0 mg, 0.63 mmol) in triethylamine (8 mL) was
14 treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged with argon
15 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (133 mg, 0.19
16 mmol) was added and the reaction mixture was stirred overnight at room
17 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
18 151.0 mg (76%) of the title compound as an orange solid.

19 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 7.6 Hz), 7.58 (2H, d, J = 7.6 Hz), 7.50
20 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 3.74
21 (1H, septet, J = 6.2 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 1.08 (6H, d,
22 J = 6.2 Hz), 0.97 (2H, m).

23 Methyl {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate

24 (**Compound 72**, General Formula 2)

25 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-
26 benzene (**Intermediate 66**, 95.0 mg, 0.45 mmol) and methyl-(4-
27 iodophenyl)-acetate (**Reagent B**, 131.0 mg, 0.45 mmol) in triethylamine (6

1 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged
2 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
3 (111 mg, 0.16 mmol) was added and the reaction mixture was stirred
4 overnight at room temperature. Column chromatography (2-8% EtOAc -
5 hexanes) afforded 110.0 mg (70%) of the title compound as an orange oil.
6 ¹H NMR (CDCl₃) δ: 7.20 (4H), 7.08 (2H, d, J = 7.0 Hz), 6.97 (2H, d, J = 7.9
7 Hz), 3.45 (1H, septet, J = 6.2 Hz), 3.41 (3H, s), 3.35 (2H, s), 0.91 (2H, m),
8 0.79 (6H, d, J = 6.2 Hz), 0.68 (2H, m).

9 4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-benzoic acid (Compound
10 73, General Formula 2)

11 Using General Procedure I; a solution of ethyl 4-[4-(1-
12 isopropoxycyclopropyl)-phenylethynyl]-benzoate (Compound 71, 110.0
13 mg, 0.32 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated
14 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and
15 stirred overnight at room temperature. Work-up afforded 89.0 mg (88%) of
16 the title compound as a yellow solid.

17 ¹H NMR (CDCl₃) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.55
18 (2H, d, J = 8.2 Hz), 7.46 (2H, d, J = 8.2 Hz), 3.73 (1H, septet, J = 6.2 Hz),
19 1.18 (2H, m), 1.04 (6H, d, J = 6.2 Hz), 0.99 (2H, m).

20 {4-[4-(1-Isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid
21 (Compound 74, General Formula 2)

22 Using General Procedure I; a solution of methyl {4-[4-(1-
23 isopropoxycyclopropyl)-phenylethynyl]-phenyl}-acetate (Compound 72,
24 80.0 mg, 0.23 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
25 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
26 and stirred overnight at room temperature. Work-up afforded 48.0 mg
27 (56%) of the title compound as a solid.

1 ¹H NMR (CDCl₃) δ: 7.20 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.09
2 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.2 Hz), 3.46 (1H, septet, J = 6.2 Hz),
3 3.37 (2H, s), 0.92 (2H, m), 0.79 (6H, d, J = 6.2 Hz), 0.67 (2H, m).

4 Benzyl 4-bromobenzoate (Intermediate 67)

5 Using General Esterification Method B; 4-bromobenzoic acid (2.01
6 g, 10.0 mmols), benzyl bromide (1.89 g, 11.1 mmols), and K₂CO₃ (1.40 g,
7 10.0 mmols) afforded 2.33 g (80%) of the title compound as a colorless
8 solid after column chromatography (3-10% EtOAc - hexanes).

9 ¹H NMR (CDCl₃) δ: 7.89 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz), 7.43
10 - 7.31 (5H), 5.33 (2H, s).

11 1-Bromo-4-(1-benzyloxyvinyl)-benzene (Intermediate 68)

12 Using General Procedure 1; benzyl 4-bromobenzoate (Intermediate
13 67, 920.0 mg, 3.16 mmols) and 6.3 mL of Tebbe's Reagent (897.0 mg, 3.16
14 mmols) afforded 640.0 mg (70%) of the title compound after column
15 chromatography (100% hexanes).

16 ¹H NMR (CDCl₃) δ: 7.55 - 7.35 (9H), 4.95 (2H, s), 4.73 (1H, d, J = 2.9 Hz),
17 4.34 (1H, d, J = 2.9 Hz).

18 1-Bromo-4-(1-benzyloxycyclopropyl)-benzene (Intermediate 69)

19 Using General Procedure 2; 1-bromo-4-(1-benzyloxyvinyl)-benzene
20 (Intermediate 68, 280.0 mg, 0.97 mmol), Et₂Zn (247.0 mg, 2.0 mmols),
21 and CH₂I₂ (536.0 mg, 2.0 mmols) in 2.0 mL Et₂O afforded 159.0 mg (53%)
22 of the title compound as a colorless solid after chromatography (2-5%
23 EtOAc - hexanes).

24 ¹H NMR (CDCl₃) δ: 7.49 - 7.24 (9H), 4.41 (2H, s), 1.29 (2H, m), 1.00 (2H,
25 m).

26 [4-(1-Benzyloxycyclopropyl)-phenylethynyl]-trimethylsilane (Intermediate
27 70)

1 Using General Procedure D; 1-bromo-4-(1-benzyloxycyclopropyl)-
2 benzene (**Intermediate 69**, 160.0 mg, 0.53 mmol) in triethylamine (5 mL)
3 was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then sparged
4 with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was
5 then added followed by dichlorobis-(triphenylphosphine)palladium(II) (37.0
6 mg, 0.05 mmol). The resulting reaction mixture was heated to 70 °C for 5d.
7 The title compound (150.0 mg, 83%) was isolated by chromatography (0 -
8 3% EtOAc - hexanes) as a pale-yellow oil.

9 ¹H NMR (CDCl₃) δ: 7.21 (3H, m), 7.09 - 7.01 (6H, m), 4.18 (2H, s), 1.07
10 (2H, m), 0.79 (2H, m), 0.02 (9H, s).

11 1-Ethynyl-4-(1-benzyloxycyclopropyl)-benzene (**Intermediate 71**)

12 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-
13 phenylethynyl]-trimethylsilane (**Intermediate 70**, 150.0 mg, 0.47 mmols) in
14 methanol (6 mL) was treated with potassium carbonate (100.0 mg, 0.72
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (115
16 mg, 100%) was used directly in the next reaction.

17 ¹H NMR (CDCl₃) δ: 7.67 - 7.50 (2H, d, J = 8.2 Hz), 7.34 - 7.26 (7H, m),
18 4.43 (2H, s), 3.07 (1H, s), 1.32 (2H, m), 1.04 (2H, m).

19 Ethyl 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-benzoate (**Compound**
20 **75, General Formula 2**)

21 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-
22 benzene (**Intermediate 71**, 60.0 mg, 0.24 mmol) and ethyl-4-iodo benzoate
23 (**Reagent A**, 72.0 mg, 0.26 mmol) in triethylamine (4 mL) was treated with
24 copper(I)iodide (17.0 mg, 0.09 mmol) and sparged with argon for 5 minutes.
25 Dichlorobis(triphenylphosphine)palladium(II) (61 mg, 0.09 mmol) was
26 added and the reaction mixture was stirred overnight at room temperature.
27 Column chromatography (2-4% EtOAc - hexanes) afforded 85.0 mg (91%)

1 of the title compound as an orange oil.

2 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.62-7.54 (4H, m), 7.39-7.26
3 (7H, m), 4.47 (2H, s), 4.40 (2H, q, J = 7.1 Hz), 1.42 (3H, t, J = 7.1 Hz), 1.36
4 (2H, m), 1.07 (2H, m).

5 Methyl {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate

6 (Compound 76, General Formula 2)

7 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-
8 benzene (Intermediate 71, 60.0 mg, 0.20 mmol) and methyl-(4-
9 iodophenyl)-acetate (Reagent B, 66.0 mg, 0.24 mmol) in triethylamine (5
10 mL) was treated with copper(I)iodide (15.0 mg, 0.08 mmol) and sparged
11 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (56
12 mg, 0.08 mmol) was added and the reaction mixture was stirred overnight at
13 room temperature. Column chromatography (2-7% EtOAc - hexanes)
14 afforded 64.0 mg (81%) of the title compound as a yellow oil.

15 ¹H NMR (CDCl₃) δ: 7.52-7.47 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s),
16 3.70 (3H, s), 3.64 (2H, s), 1.32 (2H, m), 1.06 (2H, m).

17 4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-benzoic acid (Compound
18 77, General Formula 2)

19 Using General Procedure I; a solution of ethyl 4-[4-(1-
20 benzyloxycyclopropyl)-phenylethynyl]-benzoate (Compound 75, 78.0 mg,
21 0.20 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
22 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred
23 overnight at room temperature. Work-up afforded 65.0 mg (89%) of the
24 title compound as a solid.

25 ¹H NMR (CDCl₃) δ: 7.97 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.58
26 (2H, d, J = 8.5 Hz), 7.41-7.28 (7H, m), 4.44 (2H, s), 1.33 (2H, m), 1.12 (2H,
27 m).

1 {4-[4-(1-Benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetic acid

2 **(Compound 78, General Formula 2)**

3 Using General Procedure I; a solution of methyl {4-[4-(1-
4 benzyloxycyclopropyl)-phenylethynyl]-phenyl}-acetate (**Compound 76**,
5 45.0 mg, 0.11 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
6 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
7 and stirred overnight at room temperature. Work-up afforded 35.0 mg
8 (81%) of the title compound as a pale-yellow solid.

9 ¹H NMR (CDCl₃) δ: 7.49 (4H, m), 7.37-7.25 (9H, m), 4.44 (2H, s), 3.66
10 (2H, s), 1.32 (2H, m), 1.05 (2H, m).

11 Benzyl 4-bromo-2-methylbenzoate (**Intermediate 72**)

12 Using General Esterification Method C; 2-methyl-4-bromo-benzoic
13 acid (2.15 g, 10.0 mmols) was refluxed for 3h with 10 mL SOCl₂. The
14 resulting solution concentrated under reduced pressure and the crude acyl
15 chloride was combined with benzyl alcohol (1.08 g, 10.0mmols) and
16 pyridine (1.6 mL, 20.0 mmols) to give the title compound (2.4 g, 80%) after
17 work-up and column chromatography (2-5% EtOAc - hexanes) as a
18 colorless oil.

19 ¹H NMR (CDCl₃) δ: 7.81 (1H, d, J = 8.5 Hz), 7.41-7.33 (7H, m), 5.32 (2H,
20 s), 2.57 (3H, s).

21 4-Bromo-1-(1-benzyloxyvinyl)-2-methylbenzene (**Intermediate 73**)

22 Using General Procedure 1; benzyl 4-bromo-2-methylbenzoate
23 (**Intermediate 72**, 840.0 mg, 2.77 mmols) and 5.4 mL of Tebbe's Reagent
24 (788.0 mg, 2.77 mmols) afforded 640.0 mg (76%) of the title compound
25 after column chromatography (100% hexanes).

26 ¹H NMR (CDCl₃) δ: 7.38-7.19 (8H, m), 4.88 (2H, s), 4.45 (1H, d, J = 2.6
27 Hz), 4.25 (2H, d, J = 2.6 Hz), 2.35 (3H, s).

1 4-Bromo-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate 74)

2 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-methyl-
3 benzene (**Intermediate 73**, 400.0 mg, 1.32 mmols), Et_2Zn (325.0 mg, 2.63
4 mmols), and CH_2I_2 (704.0 mg, 2.63 mmols) in 4 mL Et_2O afforded 380.0 mg
5 (90%) of the title compound as a colorless oil after chromatography (2-5%
6 EtOAc - hexanes).

7 ^1H NMR (CDCl_3) δ : 7.42-7.20 (8H, m), 4.31 (2H, s), 2.58 (3H, s), 1.25 (2H,
8 m), 0.94 (2H, m).

9 [4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane
10 (**Intermediate 75**)

11 Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-
12 methyl-benzene (**Intermediate 74**, 320.0 mg, 1.00 mmol) in triethylamine
13 (8 mL) was treated with copper(I)iodide (19.0 mg, 0.1 mmol) and then
14 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1
15 mmols) was then added followed by dichlorobis-
16 (triphenylphosphine)palladium(II) (70.0 mg, 0.05 mmol). The resulting
17 reaction mixture was heated to 70 °C for 5d. The title compound (300.0 mg,
18 89%) was isolated by chromatography (0 - 2% EtOAc - hexanes).
19 ^1H NMR (CDCl_3) δ : 7.34-7.13 (8H, m), 4.24 (2H, s), 2.52 (3H, s), 1.20
20 (2H, m), 0.88 (2H, m), 0.25 (9H, s).

21 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-methyl-benzene (Intermediate
22 76)

23 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-methyl-
24 phenylethynyl]-trimethylsilane (**Intermediate 75**, 300.0 mg, 0.95 mmols) in
25 methanol (6 mL) was treated with potassium carbonate (120.0 mg, 0.87
26 mmol) and stirred overnight at ambient temperature. The crude alkyne (185
27 mg, 79%) was used directly in the next reaction.

1 ¹H NMR (CDCl₃) δ: 7.37-7.16 (8H, m), 4.27 (2H, s), 3.07 (1H, s), 2.55
2 (3H, s), 1.21 (2H, m), 0.92 (2H, m).

3 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate
4 **(Compound 79, General Formula 2)**

5 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
6 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and ethyl-4-iodo
7 benzoate (**Reagent A**, 95.0 mg, 0.34 mmol) in triethylamine (6 mL) was
8 treated with copper(I)iodide (23.0 mg, 0.12 mmol) and sparged with argon
9 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11
10 mmol) was added and the reaction mixture was stirred overnight at room
11 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
12 68.0 mg (54%) of the title compound.

13 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz),
14 7.33-7.16 (8H, m), 4.39 (2H, q, J = 7.1 Hz), 4.29 (2H, s), 2.57 (3H, s), 1.40
15 (3H, t, J = 7.1 Hz), 1.22 (2H, m), 0.93 (2H, m).

16 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-
17 acetate **(Compound 80, General Formula 2)**

18 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
19 methyl-benzene (**Intermediate 76**, 90.0 mg, 0.34 mmol) and methyl-(4-
20 iodophenyl)-acetate (**Reagent B**, 95.0 mg, 0.34 mmol) in triethylamine (5
21 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol) and sparged
22 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (80
23 mg, 0.11 mmol) was added and the reaction mixture was stirred overnight at
24 room temperature. Column chromatography (2-4% EtOAc - hexanes)
25 afforded 90.0 mg (71%) of the title compound as a pale-yellow oil.
26 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.32-7.16 (10H, m), 4.28
27 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.56 (3H, s), 1.22 (2H, m), 0.92 (2H, m).

1 4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid

2 **(Compound 81, General Formula 2)**

3 Using General Procedure I; a solution of ethyl 4-[4-(1-
4 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 79**,
5 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
6 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)
7 and stirred overnight at room temperature. Work-up afforded 48.0 mg
8 (76%) of the title compound as a solid.

9 ¹H NMR (CDCl₃) δ: 8.10 (2H, d, J = 8.1 Hz), 7.63 (2H, d, J = 8.1 Hz), 7.44-
10 7.16 (8H, m), 4.29 (2H, m), 2.58 (3H, s), 1.24 (2H, m), 0.94 (2H, m).

11 {4-[4-(1-Benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic
12 acid (**Compound 82, General Formula 2**)

13 Using General Procedure I; a solution of methyl {4-[4-(1-
14 benzyloxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate
15 (**Compound 80**, 75.0 mg, 0.18 mmol) in ethanol (3 mL) and
16 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
17 mL of a 1N aqueous solution) and stirred overnight at room temperature.
18 Work-up afforded 30.0 mg (40%) of the title compound.

19 ¹H NMR (CDCl₃) δ: 7.51 (2H, d, J = 8.2 Hz), 7.42 (1H, s), 7.33-7.17 (9H,
20 m), 4.36 (2H, s), 3.67 (2H, s), 2.57 (3H, s), 1.23 (2H, m), 0.94 (2H, m).

21 Isopropyl 3-methyl-4-bromobenzoate (**Intermediate 77**)

22 Using General Esterification Procedure A; 4-bromo-2-methylbenzoic
23 acid (1.6 g, 7.4 mmols) was combined with isopropyl alcohol to give 1.5 g
24 (79%) of the title compound as a colorless oil.

25 ¹H NMR (CDCl₃) δ: 7.76 (1H, d, J = 8.2 Hz), 7.40 (1H, d, J = 7.4 Hz), 7.37
26 (1H, dd, J = 1.4, 8.2 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.57 (3H, s), 1.37
27 (6H, d, J = 6.2 Hz).

1 4-Bromo-1-(1-isopropoxyvinyl)-2-methyl-benzene (Intermediate 78)

2 Using General Procedure 1; isopropyl 2-methyl-4-bromobenzoate
3 (**Intermediate 77**, 800.0 mg, 3.11 mmols) and 6.2 mL of Tebbe's Reagent
4 (885.2 mg, 3.11 mmols) afforded 595.0 mg (75%) of the title compound as a
5 colorless oil after column chromatography (100% hexanes).

6 ¹H NMR (CDCl₃) δ: 7.31-7.25 (2H, m), 7.16 (1H, d, J = 8.2 Hz), 4.34 (1H,
7 septet, J = 6.0 Hz), 4.31 (1H, d, J = 2.1 Hz), 4.18 (1H, d, J = 2.1 Hz), 2.33
8 (3H, s), 1.31 (6H, d, J = 6.0 Hz).

9 4-Bromo-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (Intermediate
10 79)

11 Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-
12 methyl-benzene (**Intermediate 78**, 389.0 mg, 1.53 mmols), Et₂Zn (376.6
13 mg, 3.05 mmols), and CH₂I₂ (817.0 mg, 3.05 mmols) in 3.0 mL Et₂O
14 afforded 340.0 mg (84%) of the title compound as a colorless oil after
15 chromatography (3% EtOAc - hexanes).

16 ¹H NMR (CDCl₃) δ: 7.33 (1H, d, J = 2.3 Hz), 7.24 (1H, dd, J = 2.3, 8.2 Hz),
17 7.13 (1H, d, J = 8.2 Hz), 3.57 (1H, septet, J = 6.1 Hz), 2.49 (3H, s), 1.00
18 (2H, m), 0.97 (6H, d, J = 6.1 Hz), 0.82 (2H, m).

19 [4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-trimethylsilane
20 (Intermediate 80)

21 Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-
22 2-methyl-benzene (**Intermediate 79**, 250.0 mg, 0.95 mmol) in triethylamine
23 (8 mL) was treated with copper(I)iodide (19.0 mg, 0.10 mmol) and then
24 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1
25 mmols) was then added followed by dichlorobis-
26 (triphenylphosphine)palladium(II) (70.0 mg, 0.1 mmol). The resulting
27 reaction mixture was heated to 70 °C for 5d. The title compound (250.0 mg,

1 91%) was isolated by chromatography (0 - 3% EtOAc - hexanes).

2 ¹H NMR (CDCl₃) δ: 7.32-7.17 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.48
3 (3H, s), 1.00 (2H, m), 0.95 (6H, d, J = 6.2 Hz), 0.83 (2H, m), 0.24 (9H, s).

4 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-methyl-benzene (**Intermediate**
5 **81**)

6 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-methyl-
7 phenylethynyl]-trimethylsilane (**Intermediate 80**, 250.0 mg, 0.87 mmol) in
8 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
9 mmol) and stirred overnight at ambient temperature. The crude alkyne (180
10 mg, 98%) was used directly in the next reaction.

11 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.23 (2H, m), 3.57 (1H, septet, J = 6.2
12 Hz), 3.05 (1H, s), 2.50 (3H, s), 1.11 (2H, m), 0.96 (6H, d, J = 6.2 Hz), 0.83
13 (2H, m).

14 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate
15 (**Compound 83**, General Formula 2)

16 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-
17 3-methyl-benzene (**Intermediate 81**, 80.0 mg, 0.13 mmol) and ethyl-4-iodo
18 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was
19 treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged with argon
20 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (91 mg, 0.13
21 mmol) was added and the reaction mixture was stirred overnight at room
22 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
23 75.0 mg (56%) of the title compound as an orange solid.

24 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.39
25 (1H, s), 7.29-7.20 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.60 (1H, septet, J = 6.2
26 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87
27 (2H, m).

1 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-
2 acetate (Compound 84, General Formula 2)

3 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-
4 3-methyl-benzene (**Intermediate 81**, 100.0 mg, 0.47 mmol) and methyl-(4-
5 iodophenyl)-acetate (**Reagent B**, 129.0 mg, 0.45 mmol) in triethylamine (6
6 mL) was treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged
7 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
8 (110 mg, 0.16 mmol) was added and the reaction mixture was stirred
9 overnight at room temperature. Column chromatography (2-4% EtOAc -
10 hexanes) afforded 120.0 mg (71%) of the title compound.

11 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.5 Hz), 7.36 (1H, s), 7.29-7.22 (4H,
12 m), 3.70 (3H, s), 3.63 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.52 (3H, s),
13 1.09 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

14 4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid
15 (Compound 85, General Formula 2)

16 Using General Procedure I; a solution of ethyl 4-[4-(1-
17 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoate (**Compound 83**,
18 60.0 mg, 0.17 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was
19 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
20 and stirred overnight at room temperature. Work-up afforded 38.0 mg
21 (69%) of the title compound as a colorless solid.

22 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz),
23 7.42 (1H, s), 7.35 (2H, m), 3.59 (1H, septet, J = 6.2 Hz), 2.52 (3H, s), 1.07
24 (2H, m), 0.93 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

25 {4-[4-(1-Isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetic
26 acid (Compound 86, General Formula 2)

27 Using General Procedure I; a solution of methyl {4-[4-(1-

1 isopropoxycyclopropyl)-3-methyl-phenylethynyl]-phenyl}-acetate
2 (**Compound 84**, 100.0 mg, 0.28 mmol) in ethanol (3 mL) and
3 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
4 mL of a 1N aqueous solution) and stirred overnight at room temperature.
5 Work-up afforded 60.0 mg (62%) of the title compound as a colorless solid.
6 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 7.6 Hz), 7.36 (1H, s), 7.25 (4H, m),
7 3.65 (2H, s), 3.60 (1H, septet, J = 6.2 Hz), 2.51 (3H, s), 1.12 (2H, m), 0.97
8 (6H, d, J = 6.2 Hz), 0.86 (2H, m).

9 **2,2-Dimethylpropyl 2-methyl-4-bromobenzoate (Intermediate 82)**

10 Using General Esterification Method C; 2-methyl-4-bromo-benzoic
11 acid (1.82 g, 8.47 mmols) was refluxed for 3h with 10 mL SOCl₂. The
12 resulting solution was concentrated under reduced pressure and the crude
13 acyl chloride combined with 2,2-dimethylpropanol (0.75 g, 8.47 mmols) and
14 pyridine (1.4 mL, 16.9 mmols) to give the title compound (1.64 g, 68%)
15 after work-up and column chromatography (2-5% EtOAc - hexanes) as a
16 colorless oil.

17 ¹H NMR (CDCl₃) δ: 7.81 (1H, d, J = 8.2 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.39
18 (1H, dd, J = 2.0, 8.2 Hz), 3.99 (2H, s), 2.60 (3H, s), 1.03 (9H, s).

19 **4-Bromo-1-[1-(2,2-dimethylpropyloxy)-vinyl]-2-methyl-benzene**
20 **(Intermediate 83)**

21 Using General Procedure 1; 2,2-dimethylpropyl 2-methyl-4-
22 bromobenzoate (**Intermediate 82**, 820.0 mg, 2.87 mmols) and 5.8 mL of
23 Tebbe's Reagent (817.0 mg, 2.87 mmols) afforded 800.0 mg (98%) of the
24 title compound as a colorless oil after column chromatography (100%
25 hexanes). ¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J =
26 2.0, 8.2 Hz), 7.18 (1H, d, J = 8.2 Hz), 4.27 (1H, d, J = 2.1 Hz), 4.10 (1H, d,
27 J = 2.1 Hz), 3.43 (2H, s), 2.33 (3H, s), 0.98 (9H, s).

1 4-Bromo-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene

2 **(Intermediate 84)**

3 Using General Procedure 2; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-
4 cyclopropyl]-2-methyl-benzene (**Intermediate 83**, 400.0 mg, 1.43 mmols),
5 Et₂Zn (353.2 mg, 2.86 mmols), and CH₂I₂ (760.0 mg, 2.86 mmols) in 3.0
6 mL Et₂O afforded 370.0 mg (87%) of the title compound as a colorless oil
7 after chromatography (3% EtOAc - hexanes).

8 ¹H NMR (CDCl₃) δ: 7.36 (1H, s), 7.27 (1H, d, J = 8.5 Hz), 7.09 (1H, d, J =
9 7.9 Hz), 2.86 (2H, s), 2.52 (3H, s), 1.08 (2H, m), 0.83 (2H, m), 0.80 (9H, s).

10 [4-[1-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]]-

11 trimethylsilane (Intermediate 84a)

12 Using General Procedure D; 4-bromo-1-[1-(2,2-dimethylpropyloxy)-
13 cyclopropyl]-2-methyl-benzene (**Intermediate 84**, 255.0 mg, 0.86 mmol) in
14 triethylamine (8 mL) was treated with copper(I)iodide (17.0 mg, 0.09 mmol)
15 and then sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g,
16 7.1 mmols) was then added followed by dichlorobis-
17 (triphenylphosphine)palladium(II) (63.0 mg, 0.09 mmol). The resulting
18 reaction mixture was heated to 70 °C for 5d. The title compound (220.0 mg,
19 81%) was isolated by chromatography (1-2% EtOAc - hexanes).

20 ¹H NMR (CDCl₃) δ: 7.30 (1H, s), 7.21 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J =
21 8.6 Hz), 2.80 (2H, s), 2.47 (3H, s), 1.05 (2H, m), 0.82 (2H, m), 0.75 (9H, s),
22 0.24 (9H, s).

23 4-Ethynyl-1-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-2-methyl-benzene

24 **(Intermediate 85)**

25 Using General Procedure E; [4-[1-[1-(2,2-dimethylpropyloxy)-
26 cyclopropyl]]-3-methyl-phenylethynyl]-trimethylsilane (**Intermediate 84a**,
27 220.0 mg, 0.83 mmol) in methanol (10 mL) was treated with potassium

1 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient
2 temperature. The crude alkyne (155 mg, 76%) was used directly in the next
3 reaction.

4 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.24 (1H, d, J = 7.1 Hz), 7.15 (1H, d, J =
5 7.1 Hz), 3.04 (1H, s), 2.83 (2H, s), 2.49 (3H, s), 1.06 (2H, m), 0.83 (2H, m),
6 0.76 (9H, s).

7 Ethyl 4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-
8 phenylethynyl]-benzoate (Compound 87, General Formula 2)

9 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-
10 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and
11 ethyl-4-iodo benzoate (**Reagent A**, 86.0 mg, 0.31 mmol) in triethylamine (5
12 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged
13 with argon for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II)
14 (78 mg, 0.11 mmol) was added and the reaction mixture was stirred
15 overnight at room temperature. Column chromatography (2-4% EtOAc -
16 hexanes) afforded 60.0 mg (50%) of the title compound as an orange solid.
17 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.38
18 (1H, s), 7.30 (1H, dd, J = 1.1, 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 4.38 (2H, q,
19 J = 7.1 Hz), 2.84 (2H, s), 2.52 (3H, s), 1.40 (3H, t, J = 7.1 Hz), 1.07 (2H, m),
20 0.84 (2H, m), 0.77 (9H, s).

21 Methyl {4-[4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-
22 phenylethynyl]-phenyl}-acetate (Compound 88, General Formula 2)

23 Using General Procedure F; 4-ethynyl-1-[1-(2,2-dimethylpropyloxy)-
24 cyclopropyl]-3-methyl-benzene (**Intermediate 85**, 75.0 mg, 0.31 mmol) and
25 methyl-(4-iodophenyl)-acetate (**Reagent B**, 86.0 mg, 0.31 mmol) in
26 triethylamine (6 mL) was treated with copper(I)iodide (21.0 mg, 0.11 mmol)
27 and sparged with argon for 5 minutes.

1 Dichlorobis(triphenylphosphine)palladium(II) (78 mg, 0.11 mmol) was
2 added and the reaction mixture was stirred overnight at room temperature.
3 Column chromatography (2-4% EtOAc - hexanes) afforded 100.0 mg (83%)
4 of the title compound.

5 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 7.9 Hz), 7.36-7.24 (4H, m), 7.18 (1H,
6 d, J = 7.9 Hz), 3.70 (3H, s), 3.63 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07
7 (2H, m), 0.83 (2H, m), 0.77 (9H, s).

8 4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
9 benzoic acid (Compound 89, General Formula 2)

10 Using General Procedure I; a solution of ethyl 4-[4-[1-(2,2-
11 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-benzoate
12 (Compound 87, 60.0 mg, 0.15 mmol) in ethanol (3 mL) and
13 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
14 mL of a 1N aqueous solution) and stirred overnight at room temperature.
15 Work-up afforded 24.0 mg (43%) of the title compound as a colorless solid.
16 ¹H NMR (CDCl₃) δ: 8.06 (2H, d, J = 7.9 Hz), 7.65 (2H, d, J = 7.9 Hz), 7.42
17 (1H, s), 7.33 (2H, m), 2.89 (2H, s), 2.53 (3H, s), 1.07 (2H, m), 0.90 (2H, m),
18 0.77 (9H, s).

19 {4-[4-[1-(2,2-Dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
20 phenyl}-acetic acid (Compound 90, General Formula 2)

21 Using General Procedure I; a solution of methyl {4-[4-[1-(2,2-
22 dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetate
23 (Compound 88, 95.0 mg, 0.24 mmol) in ethanol (3 mL) and
24 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
25 mL of a 1N aqueous solution) and stirred overnight at room temperature.
26 Work-up afforded 49.0 mg (53%) of the title compound as a colorless solid.
27 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.36 (1H, s), 7.27 (3H, m),

1 7.18 (1H, d, $J = 7.9$ Hz), 3.66 (2H, s), 2.84 (2H, s), 2.51 (3H, s), 1.07 (2H,
2 m), 0.83 (2H, m), 0.77 (9H, s).

3 Benzyl 4-bromo-2-ethyl-benzoate (**Intermediate 86**)

4 Using General Esterification Method B; 4-bromo-2-ethyl-benzoic
5 acid (0.98 g, 4.25 mmols), benzyl bromide (0.80 g, 4.68 mmols), and K_2CO_3
6 (0.64 g, 4.68 mmols) afforded 1.0 g (74%) of the title compound after
7 column chromatography (0-3% EtOAc - hexanes).

8 1H NMR ($CDCl_3$) δ : 7.76 (1H, d, $J = 8.5$ Hz), 7.41-7.33 (7H, m), 5.32 (2H,
9 s), 2.95 (2H, q, $J = 7.6$ Hz), 1.20 (3H, t, $J = 7.6$ Hz).

10 4-Bromo-1-(1-benzyloxyvinyl)-2-ethyl-benzene (**Intermediate 87**)

11 Using General Procedure 1; benzyl 4-bromo-2-ethylbenzoate
12 (**Intermediate 86**, 1.20 g, 3.78 mmols) and 7.6 mL of Tebbe's Reagent
13 (1.08 g, 3.78 mmols) afforded 800.0 mg (66%) of the title compound after
14 column chromatography (100% hexanes).

15 1H NMR ($CDCl_3$) δ : 7.37-7.17 (8H, m), 4.88 (2H, s), 4.43 (1H, d, $J = 2.1$
16 Hz), 4.25 (1H, d, $J = 2.1$ Hz), 2.71 (2H, q, $J = 7.6$ Hz), 1.18 (3H, t, $J = 7.6$
17 Hz).

18 4-Bromo-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (**Intermediate 88**)

19 Using General Procedure 2; 4-bromo-1-(1-benzyloxyvinyl)-2-ethyl-
20 benzene (**Intermediate 87**, 330.0 mg, 1.04 mmols), Et_2Zn (257.0 mg, 2.08
21 mmols), and CH_2I_2 (557.0 mg, 2.08 mmols) in 4 mL Et_2O afforded 241.0 mg
22 (70%) of the title compound as a colorless oil after chromatography (2-5%
23 EtOAc - hexanes).

24 1H NMR ($CDCl_3$) δ : 7.43-7.15 (8H, m), 4.27 (2H, s), 3.00 (2H, q, $J = 7.6$
25 Hz), 1.29-1.21 (5H, m), 0.90 (2H, m).

26 [4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane

27 (**Intermediate 89**)

1 Using General Procedure D; 4-bromo-1-(1-benzyloxycyclopropyl)-2-
2 ethyl-benzene (**Intermediate 88**, 220.0 mg, 0.66 mmol) in triethylamine (8
3 mL) was treated with copper(I)iodide (14.0 mg, 0.07 mmol) and then
4 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1
5 mmols) was then added followed by dichlorobis-
6 (triphenylphosphine)palladium(II) (50.0 mg, 0.07 mmol). The resulting
7 reaction mixture was heated to 70 °C for 5d. The title compound was
8 isolated by chromatography (0 - 2% EtOAc - hexanes).

9 ¹H NMR (CDCl₃) δ: 7.41-7.13 (8H, m), 4.24 (2H, s), 2.98 (2H, q, J = 7.6
10 Hz), 1.25 (3H, t, J = 7.6 Hz), 1.20 (2H, m), 0.90 (2H, m), 0.26 (9H, s).
11 4-Ethynyl-1-(1-benzyloxycyclopropyl)-2-ethyl-benzene (**Intermediate 90**)

12 Using General Procedure E; [4-(1-benzyloxycyclopropyl)-3-ethyl-
13 phenylethynyl]-trimethylsilane (**Intermediate 89**, 240 mg, 0.69 mmol) in
14 methanol (6 mL) was treated with potassium carbonate (10.0 mg, 0.72
15 mmol) and stirred overnight at ambient temperature. The crude alkyne (190
16 mg, 99%) was used directly in the next reaction. ¹H NMR (CDCl₃) δ: 7.43-
17 7.15 (8H, m), 4.27 (2H, s), 3.08 (1H, s), 3.01 (2H, q, J = 7.6 Hz), 1.26 (3H,
18 t, J = 7.6 Hz), 1.22 (2H, m), 0.92 (2H, m).

19 Ethyl 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate
20 (**Compound 91**, General Formula 2)

21 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
22 ethyl-benzene (**Intermediate 90**, 90.0 mg, 0.33 mmol) and ethyl-4-iodo
23 benzoate (**Reagent A**, 100.0 mg, 0.36 mmol) in triethylamine (5 mL) was
24 treated with copper(I)iodide (21.0 mg, 0.11 mmol) and sparged with argon
25 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (77 mg, 0.11
26 mmol) was added and the reaction mixture was stirred overnight at room
27 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded

1 100.0 mg (72%) of the title compound.

2 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (2H, d, J = 7.9 Hz), 7.49
3 (1H, s), 7.36-7.16 (7H, m), 4.38 (2H, q, J = 7.1 Hz), 4.28 (2H, s), 3.04 (2H,
4 q, J = 7.6 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H,
5 m), 0.94 (2H, m).

6 Methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-
7 acetate (Compound 92, General Formula 2)

8 Using General Procedure F; 1-ethynyl-4-(1-benzyloxycyclopropyl)-3-
9 ethyl-benzene (**Intermediate 90**, 107.0 mg, 0.39 mmol) and methyl-(4-
10 iodophenyl)-acetate (**Reagent B**, 110.0 mg, 0.39 mmol) in triethylamine (5
11 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged
12 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91
13 mg, 0.13 mmol) was added and the reaction mixture was stirred overnight at
14 room temperature. Column chromatography (2-4% EtOAc - hexanes)
15 afforded 130.0 mg (79%) of the title compound as a pale-yellow oil.
16 ¹H NMR (CDCl₃) δ: 7.49 (3H, m), 7.32-7.16 (9H, m), 4.28 (2H, s), 3.71
17 (3H, s), 3.64 (2H, s), 3.03 (2H, q, J = 7.6 Hz), 1.32-1.23 (5H, m), 0.94 (2H,
18 m).

19 4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid
20 (Compound 93, General Formula 2)

21 Using General Procedure I; a solution of ethyl 4-[4-(1-
22 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 91**,
23 100.0 mg, 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
24 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
25 and stirred overnight at room temperature. Work-up and purification by
26 HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound as a
27 colorless solid.

¹H NMR (CDCl₃) δ: 8.10 (2H, d, J = 8.5 Hz), 7.64 (2H, d, J = 8.5 Hz), 7.50 (1H, s), 7.35-7.16 (7H, m), 4.29 (2H, s), 3.04 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J = 7.6 Hz), 1.25 (2H, m), 0.95 (2H, m).
{4-[4-(1-Benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid
(Compound 94, General Formula 2)

Using General Procedure I; a solution of methyl {4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate (Compound 92, 130.0 mg, 0.31 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight at room temperature. Work-up and purification by HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound.
¹H NMR (CDCl₃) δ: 7.49 (3H, m), 7.31-7.16 (9H, m), 4.28 (2H, s), 3.66 (2H, s), 3.02 (2H, q, J = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.23 (2H, m), 0.94 (2H, m).

Isopropyl 2-ethyl-4-bromobenzoate (Intermediate 91)

Using General Esterification Procedure A; 4-bromo-2-ethyl-benzoic acid (2.25 g, 9.9 mmols) was combined with isopropyl alcohol to give the title compound as a colorless oil after column chromatography (2% EtOAc-hexanes).

¹H NMR (CDCl₃) δ: 7.69 (1H, d, J = 8.5 Hz), 7.41 (1H, s), 7.36 (1H, d, J = 8.5 Hz), 5.23 (1H, septet, J = 6.2 Hz), 2.95 (2H, q, J = 7.6 Hz), 1.37 (6H, d, J = 6.2 Hz), 1.23 (3H, t, J = 7.6 Hz).

4-Bromo-1-(1-isopropoxyvinyl)-2-ethyl-benzene (Intermediate 92)

Using General Procedure 1; isopropyl 2-ethyl-4-bromobenzoate (Intermediate 91, 1.21 g, 4.46 mmols) and 8.9 mL of Tebbe's Reagent (1.27 g, 4.46 mmols) afforded 570.0 mg (75%) of the title compound after column chromatography (100% hexanes).

1 ¹H NMR (CDCl₃) δ: 7.36 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 2.0, 8.0 Hz),
2 7.17 (1H, d, J = 8.0 Hz), 4.39 (1H, septet, J = 6.2 Hz), 4.31 (1H, d, J = 2.1
3 Hz), 4.26 (1H, d, J = 2.1 Hz), 2.73 (2H, q, J = 7.6 Hz), 1.35 (6H, d, J = 6.2
4 Hz), 1.24 (3H, t, J = 7.6 Hz).

5 4-Bromo-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 93)

6 Using General Procedure 2; 4-bromo-1-(1-isopropoxyvinyl)-2-ethyl-
7 benzene (Intermediate 92, 570.0 mg, 2.11 mmols), Et₂Zn (521.0 mg, 4.22
8 mmols), and CH₂I₂ (1.13 g, 4.22 mmols) in 7.0 mL Et₂O afforded 500.0 mg
9 (85%) of the title compound as a colorless oil after chromatography (3%
10 EtOAc - hexanes).

11 ¹H NMR (CDCl₃) δ: 7.39 (1H, d, J = 2.1 Hz), 7.25 (1H, dd, J = 2.1, 8.1 Hz),
12 7.15 (1H, d, J = 8.1 Hz), 3.59 (1H, septet, J = 6.2 Hz), 2.97 (2H, q, J = 7.6
13 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.11 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.83
14 (2H, m).

15 [4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-trimethylsilane
16 (Intermediate 94)

17 Using General Procedure D; 4-bromo-1-(1-isopropoxycyclopropyl)-
18 2-ethyl-benzene (Intermediate 93, 300.0 mg, 1.07 mmol) in triethylamine
19 (8 mL) was treated with copper(I)iodide (20.0 mg, 0.11 mmol) and then
20 sparged with argon for 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1
21 mmols) was then added followed by dichlorobis-
22 (triphenylphosphine)palladium(II) (75.0 mg, 0.11 mmol). The resulting
23 reaction mixture was heated to 70 °C for 5d. The title compound (320.0 mg,
24 99%) was isolated by chromatography (0 - 2% EtOAc - hexanes) as an
25 orange oil.

26 ¹H NMR (CDCl₃) δ: 7.37-7.21 (3H, m), 3.56 (1H, septet, J = 6.2 Hz), 2.96
27 (2H, q, J = 7.6 Hz), 1.27 (3H, t, J = 7.6 Hz), 1.10 (2H, m), 0.94 (6H, d, J =

1 6.2 Hz), 0.84 (2H, m), 0.25 (9H, s):

2 4-Ethynyl-1-(1-isopropoxycyclopropyl)-2-ethyl-benzene (Intermediate 95)

3 Using General Procedure E; [4-(1-isopropoxycyclopropyl)-3-ethyl-
4 phenylethynyl]-trimethylsilane (**Intermediate 94**, 330.0 mg, 1.10 mmols) in
5 methanol (10 mL) was treated with potassium carbonate (150.0 mg, 1.10
6 mmol) and stirred overnight at ambient temperature. The crude alkyne (238
7 mg, 95%) was used directly in the next reaction.

8 ¹H NMR (CDCl₃) δ: 7.40-7.22 (3H, m), 3.59 (1H, septet, J = 6.2 Hz), 3.07
9 (1H, s), 2.97 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz), 1.12 (2H, m), 0.96
10 (6H, d, J = 6.2 Hz), 0.85 (2H, m).

11 Ethyl 4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate
12 (**Compound 95, General Formula 2**)

13 Using General Procedure F; 4-ethynyl-1-(1-isopropoxycyclopropyl)-
14 3-ethyl-benzene (**Intermediate 95**, 108.0 mg, 0.47 mmol) and ethyl-4-iodo
15 benzoate (**Reagent A**, 130.0 mg, 0.47 mmol) in triethylamine (5 mL) was
16 treated with copper(I)iodide (30.0 mg, 0.16 mmol) and sparged with argon
17 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (110 mg, 0.16
18 mmol) was added and the reaction mixture was stirred overnight at room
19 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
20 125.0 mg (71%) of the title compound as an oil.

21 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.46
22 (1H, s), 7.33-7.26 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.62 (1H, septet, J = 6.2
23 Hz), 3.01 (2H, q, J = 7.6 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.1
24 Hz), 1.14 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.88 (2H, m).

25 Methyl {4-[4-(1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-
26 acetate (Compound 96, General Formula 2)

27 Using General Procedure F; 1-ethynyl-4-(1-isopropoxycyclopropyl)-

1 3-ethyl-benzene (**Intermediate 95**, 130.0 mg, 0.57 mmol) and methyl-(4-
2 iodophenyl)-acetate (**Reagent B**, 157.0 mg, 0.57 mmol) in triethylamine (5
3 mL) was treated with copper(I)iodide (36.0 mg, 0.19 mmol) and sparged
4 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
5 (133 mg, 0.19 mmol) was added and the reaction mixture was stirred
6 overnight at room temperature. Column chromatography (2-5% EtOAc -
7 hexanes) afforded 150.0 mg (70%) of the title compound as an orange oil.
8 ¹H NMR (CDCl₃) δ: 7.50-7.44 (3H, m), 7.27 (4H, m), 3.70 (3H, s), 3.64
9 (2H, s), 3.62 (1H, septet, J = 6.2 Hz), 3.00 (2H, q, J = 7.6 Hz), 1.30 (3H, t, J
10 = 7.6 Hz), 1.13 (2H, m), 0.97 (6H, d, J = 6.2 Hz), 0.87 (2H, m).
11 4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoic acid
12 (**Compound 97**, General Formula 2)

13 Using General Procedure I; a solution of ethyl 4-[4-(1-
14 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-benzoate (**Compound 95**,
15 110.0 mg, 0.29 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
16 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
17 and stirred overnight at room temperature. Work-up and isolation by HPLC
18 (partisil 10-pac, 10% H₂O/CH₃CN) afforded the title compound as a
19 colorless solid.
20 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),
21 7.49 (1H, s), 7.40-7.34 (2H, m), 3.61 (1H, septet, J = 6.2 Hz), 3.01 (2H, q, J
22 = 7.6 Hz), 1.29 (3H, t, J = 7.6 Hz), 1.08 (2H, m), 0.93 (6H, d, J = 6.2 Hz),
23 0.88 (2H, m).

24 {4-[4-(1-Isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic
25 acid (**Compound 98**, General Formula 2)

26 Using General Procedure I; a solution of methyl {4-[4-(1-
27 isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetate

1 (Compound 96, 156.0 mg, 0.41 mmol) in ethanol (3 mL) and
2 tetrahydrofuran (3 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
3 mL of a 1N aqueous solution) and stirred overnight at room temperature.
4 Work-up and isolation by HPLC (partisil 10-pac, 10% H₂O/CH₃CN)
5 afforded 85.0 mg (57%) of the title compound.

6 ¹H NMR (CDCl₃) δ: 7.54-7.48 (3H, m), 7.34-7.27 (4H, m), 3.68 (2H, s),
7 3.66 (1H, septet, J = 6.2 Hz), 3.03 (2H, q, J = 7.6 Hz), 1.33 (2H, t, J = 7.6
8 Hz), 1.17 (2H, m), 1.01 (6H, d, J = 6.2 Hz), 0.90 (2H, m).

9 (4-Bromo-3-isopropyl-phenoxy)-triisopropyl-silane (Intermediate 96)

10 To a solution of 4-bromo-3-isopropylphenol (880.0 mg, 4.09 mmols)
11 and imidazole (417.0 mg, 6.13 mmols) in 10 mL DMF was added chloro-
12 triisopropylsilane (946.0 mg, 4.90 mmols). After stirring overnight at room
13 temperature the solution was diluted with H₂O and extracted with EtOAc.
14 The combined organic layers were washed with H₂O and saturated aqueous
15 NaCl before being dried (MgSO₄) and concentrated under reduced pressure.
16 The title compound, 1.30 g (92%), was isolated by column chromatography
17 (1-2% EtOAc-hexanes) as a colorless oil.

18 ¹H NMR (CDCl₃) δ: 7.34 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 2.9 Hz), 6.59
19 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.33-1.21 (3H, m),
20 1.24 (6H, d, J = 7.0 Hz), 1.13 (18H, d, J = 7.0 Hz).

21 Ethyl 2-isopropyl-4-triisopropylsilanyloxy-benzoate (Intermediate 97)

22 To a solution of (4-bromo-3-isopropyl-phenoxy)-triisopropyl-silane
23 (Intermediate 96, 1.3 g, 3.8 mmols) in 15 mL Et₂O cooled to -78 °C was
24 added 4.9 mL of *tert*-butyllithium in pentane (532.0 mg, 8.3 mmols; 1.7 M).
25 After stirring for 30 minutes ethyl chloroformate (832.0 mg, 7.8 mmols) was
26 added. The resulting solution was warmed to room temperature and
27 quenched by the addition of saturated aqueous NH₄Cl. The mixture was

1 extracted with EtOAc and the combined organic layers dried (MgSO₄)
2 concentrated under reduced pressure and the residue chromatographed (4%
3 EtOAc-hexanes) to give 1.09 g (85%) of the title compound as a colorless
4 oil.
5 ¹H NMR (CDCl₃) δ: 7.72 (1H, d, J = 8.5 Hz), 6.87 (1H, d, J = 2.3 Hz), 6.69
6 (1H, dd, J = 2.3, 8.5 Hz), 3.88 (1H, septet; J = 7.1 Hz), 4.30 (2H, q, J = 7.1
7 Hz), 1.36 (3H, t, J = 7.1 Hz), 1.31-1.17 (9H, m), 1.09 (18H).
8 [4-(1-Ethoxyvinyl)-3-isopropyl-phenoxy]-triisopropyl-silane (Intermediate
9 98)

10 Using General Procedure 1; ethyl 2-isopropyl-4-
11 triisopropylsilanyloxy-benzoate (Intermediate 97, 450.0 mg, 1.34 mmols)
12 and 2.0 mL of Tebbe's Reagent (398.0 mg, 1.40 mmols) afforded the title
13 compound after column chromatography (100% hexanes).
14 ¹H NMR (CDCl₃) δ: 7.11 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 2.3 Hz), 6.63
15 (1H, dd, J = 2.3, 8.2 Hz), 4.23 (1H, d, J = 1.7 Hz), 4.10 (1H, d, J = 1.7 Hz),
16 3.86 (2H, q, J = 7.0 Hz), 3.16 (1H, septet, J = 7.0 Hz), 1.35 (3H, t, J = 7.1
17 Hz), 1.28-1.19 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.11 (18H).
18 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenoxy]-triisopropyl-silane
19 (Intermediate 99)

20 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-isopropyl-
21 phenoxy]-triisopropyl-silane (Intermediate 98, 300.0 mg, 0.83 mmols),
22 Et₂Zn (325.0 mg, 2.63 mmols), and CH₂I₂ (704.0 mg, 2.63 mmols) in 5.0
23 mL Et₂O afforded 270.0 mg (86%) of the title compound as a colorless oil
24 after chromatography (0.5-2.5% EtOAc - hexanes).
25 ¹H NMR (CDCl₃) δ: 7.06 (1H, d, J = 8.2 Hz), 6.81 (1H, d, J = 2.6 Hz), 6.59
26 (1H, dd, J = 2.6, 8.2 Hz), 3.76 (1H, septet, J = 7.0 Hz), 3.25 (2H, q, J = 7.0
27 Hz), 1.30-1.20 (3H, m), 1.19 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.10 (18H),

1 1.02 (2H, t, J = 7.0 Hz), 0.82 (2H, m).

2 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenol (Intermediate 100)

3 To a solution of [4-(1-ethoxycyclopropyl)-3-isopropyl-phenoxy]-
4 triisopropyl-silane (**Intermediate 99**, 360.0 mg, 0.96mmol) in 3 mL THF at
5 0 °C was added tetrabutylammonium fluoride (625.0 mg, 2.39 mmols, 2.4
6 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30
7 minutes and then quenched by the addition of H₂O. The mixture was
8 extracted with EtOAc and the combined organic layers were washed with
9 H₂O and saturated aqueous NaCl before being dried (MgSO₄) and
10 concentrated under reduced pressure. The title compound (180 mg, 86%)
11 was isolated from the residue by column chromatography (4-10% EtOAc-
12 hexanes) as a colorless solid.

13 ¹H NMR (CDCl₃) δ: 7.13 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 2.6 Hz), 6.57
14 (1H, dd, J = 2.6, 8.2 Hz), 5.48 (1H, s), 3.79 (1H, septet, J = 7.0 Hz), 3.32
15 (2H, q, J = 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 1.12 (2H, m), 1.05 (3H, t, J =
16 7.0 Hz), 0.84 (2H, m).

17 4-(1-Ethoxycyclopropyl)-3-isopropyl-phenyl 1,1,1-trifluoromethanesulfonate
18 (**Intermediate 101**)

19 A solution of 4-(1-ethoxycyclopropyl)-3-isopropyl-phenol
20 (**Intermediate 100**, 172.0 mg, 0.78 mmol) in 5 mL of CH₂Cl₂ was cooled to
21 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-
22 chloropyridine (321.0 mg, 0.82 mmol) and triethylamine (240.0 mg, 2.4
23 mmols). The resulting solution was warmed to room temperature and stirred
24 overnight. The reaction was quenched by the addition of H₂O and the
25 mixture extracted with EtOAc and the combined organic layers were washed
26 with 10% aqueous HCl, saturated aqueous NaHCO₃, H₂O, and saturated
27 aqueous NaCl. The solution was dried (MgSO₄) and concentrated under

1 reduced pressure. The title compound was isolated by column
2 chromatography (2-4% EtOAc-hexanes) as a colorless oil, 240.0 mg, 87%.
3 ¹H NMR (CDCl₃) δ: 7.31 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.00
4 (1H, dd, J = 2.6, 8.6 Hz), 3.87 (1H, septet, J = 7.0 Hz), 2.38 (2H, q, J = 7.0
5 Hz), 1.24 (6H, d, J = 7.0 Hz), 1.15 (2H, m), 1.04 (3H, t, J = 7.0 Hz), 0.86
6 (2H, m).

7 [4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-trimethylsilane
8 **(Intermediate 102)**

9 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-isopropyl-
10 phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 101**, 240.0 mg, 0.68
11 mmol) in triethylamine (2 mL) and DMF (6 mL) was sparged with argon for
12 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added
13 followed by dichlorobis-(triphenylphosphine)palladium(II) (38.0 mg, 0.05
14 mmol). The resulting reaction mixture was heated to 95 °C for 5d. The title
15 compound, 200.0 mg (99%), was isolated by chromatography (0 - 2%
16 EtOAc - hexanes) as an orange oil.

17 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 1.7 Hz), 7.25 (1H, dd, J = 1.7, 7.9 Hz),
18 7.16 (1H, d, J = 7.9 Hz), 3.80 (1H, septet, J = 6.8 Hz), 3.26 (2H, q, J = 7.0
19 Hz), 1.24 (6H, d, J = 6.8 Hz), 1.24-1.10 (2H, m), 1.03 (3H, t, J = 7.0 Hz),
20 0.87 (2H, s), 0.26 (9H, s).

21 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-isopropylbenzene (**Intermediate 103**)

22 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-isopropyl-
23 phenylethynyl]-trimethylsilane (**Intermediate 102**, 210.0 mg, 0.70 mmol) in
24 methanol (10 mL) was treated with potassium carbonate (100.0 mg, 0.72
25 mmol) and stirred overnight at ambient temperature. The crude alkyne was
26 used directly in the next reaction.

27 ¹H NMR (CDCl₃) δ: 7.47 (1H, d, J = 1.7 Hz), 7.23 (1H, dd, J = 1.7, 7.6 Hz),

1 7.19 (1H, d, J = 7.6 Hz), 3.80 (1H, septet, J = 7.0 Hz), 3.27 (1H, q, J = 7.0
2 Hz), 3.07 (1H, s), 1.23 (6H, d, J = 7.0 Hz), 1.13 (2H, m), 1.03 (3H, t, J = 7.0
3 Hz), 0.85 (2H, m).

4 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate
5 **(Compound 99, General Formula 2)**

6 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-
7 isopropylbenzene (**Intermediate 103**, 50.0 mg, 0.22 mmol) and ethyl-4-iodo
8 benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL) was
9 treated with copper(I)iodide (14.0 mg, 0.07 mmol) and sparged with argon
10 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (51 mg, 0.07
11 mmol) was added and the reaction mixture was stirred overnight at room
12 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded
13 28.0 mg (34%) of the title compound.

14 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.51
15 (1H, d, J = 1.7 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz), 7.21 (1H, d, J = 7.9 Hz),
16 4.38 (2H, q, J = 7.1 Hz), 3.83 (1H, septet, J = 6.7 Hz), 3.29 (2H, q, J = 7.0
17 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J = 6.7 Hz), 1.14 (2H, m), 1.04
18 (3H, t, J = 7.0 Hz), 0.87 (2H, m).

19 Methyl {4-[4-(1-ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-
20 acetate (**Compound 100, General Formula 2**)

21 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-
22 isopropylbenzene (**Intermediate 103**, 120.0 mg, 0.52 mmol) and methyl-(4-
23 iodophenyl)-acetate (**Reagent B**, 150.0 mg, 0.52 mmol) in triethylamine (8
24 mL) was treated with copper(I)iodide (32.0 mg, 0.17 mmol) and sparged
25 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
26 (121 mg, 0.17 mmol) was added and the reaction mixture was stirred
27 overnight at room temperature. Column chromatography (2-5% EtOAc -
28 hexanes) afforded 140.0 mg (71%) of the title compound as a pale-yellow

1 oil.

2 ¹H NMR (CDCl₃) δ: 7.53 (3H, m), 7.31-7.23 (4H, m), 3.86 (1H, septet, J =
3 6.7 Hz), 3.73 (3H, s), 3.67 (2H, s), 3.33 (2H, q, J = 7.0 Hz), 1.30 (6H, d, J =
4 6.7 Hz), 1.15 (2H, m), 1.08 (3H, t, J = 7.0 Hz), 0.90 (2H, m).

5 4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoic acid
6 **(Compound 101, General Formula 2)**

7 Using General Procedure I; A solution of ethyl 4-[4-(1-
8 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-benzoate (**Compound 99**,
9 28.0 mg, 0.07 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was
10 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
11 and stirred overnight at room temperature. Work-up afforded 24 mg (92%)
12 the title compound as a pale-yellow solid.

13 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz),
14 7.58 (1H, s), 7.33 (2H, m), 3.87 (1H, m), 2.27 (2H, q, J = 7.0 Hz), 1.26 (6H,
15 d, J = 6.7 Hz), 1.09 (2H, m), 0.99 (3H, t, J = 7.0 Hz), 0.88 (2H, m).

16 {4-[4-(1-Ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetic
17 acid (**Compound 102, General Formula 2**)

18 Using General Procedure I; a solution of methyl {4-[4-(1-
19 ethoxycyclopropyl)-3-isopropyl-phenylethynyl]-phenyl}-acetate
20 (**Compound 100**, 130.0 mg, 0.35 mmol) in ethanol (5 mL) and
21 tetrahydrofuran (5 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0
22 mL of a 1N aqueous solution) and stirred at 50 °C for 4h. Work-up and
23 isolation by HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded 88.0 mg
24 (70%) of the title compound.

25 ¹H NMR (CDCl₃) δ: 7.50 (3H, m), 7.28-7.19 (4H, m), 3.82 (1H, m), 3.65
26 (2H, s), 3.29 (2H, q, J = 7.0 Hz), 1.25 (6H, d, J = 6.7 Hz), 1.14 (2H, m),
27 1.04 (3H, t, J = 7.0 Hz), 0.86 (2H, m).

1 4-Bromo-3-*tert*-butylphenol (Intermediate 104)

2 To a mixture of 3-*tert*-butyl-methoxy benzene (1.00 g, 6.09 mmols)
3 in CCl₄ (20 mL), molecular sieves, and silica gel was added *N*-
4 bromosuccinimide (1.19 g, 6.70 mmols). This mixture was stirred at 55 °C
5 for 48h. The resulting mixture was cooled to room temperature, filtered to
6 remove the solids, and the filtrate diluted with EtOAc. This solution was
7 washed with H₂O, 10% aqueous HCl, H₂O, saturated aqueous NaHCO₃ and
8 saturated aqueous NaCl before being dried (MgSO₄) and concentrated under
9 reduced pressure. Column chromatography (2.5% EtOAc-hexanes)
10 afforded 1.15 g (78%) of a 3 to 1 mixture of 1-bromo-2-*tert*-butyl methoxy
11 benzene and 1-bromo-2-methoxy-4-*tert*-butyl benzene as a colorless oil.

12 A solution of the isomeric methoxy compounds in 10 mL of CH₂Cl₂
13 was cooled to 0 °C and treated with a solution (18.5 mL) of BBr₃ in CH₂Cl₂
14 (4.63 g, 18.5 mmols). After 10 minutes the solution was warmed to room
15 temperature, stirred for 1h, and then quenched with H₂O. The mixture was
16 extracted with EtOAc and the combined organic layers washed with
17 saturated aqueous NaCl, dried (MgSO₄), and concentrated under reduced
18 pressure. The title compound was isolated, 1.17 g (59%), by column
19 chromatography (2.5-5% EtOAc-hexanes).

20 ¹H NMR (CDCl₃) δ: 7.39 (1H, d, J = 8.5 Hz), 6.96 (1H, d, J = 2.9 Hz), 6.54
21 (1H, dd, J = 2.9, 8.5 Hz), 1.46 (9H, s).

22 (4-Bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane (Intermediate 105)

23 To a solution of 4-bromo-3-*tert*-butylphenol (Intermediate 104, 1.17
24 g, 5.10 mmols) and imidazole (520.0 mg, 7.65 mmols) in 10 mL DMF was
25 added chloro-triisopropylsilane (1.18 g, 6.10 mmols). After stirring
26 overnight at room temperature the solution was diluted with H₂O and
27 extracted with EtOAc. The combined organic layers were washed with H₂O

1 and saturated aqueous NaCl before being dried (MgSO₄) and concentrated
2 under reduced pressure. The title compound, 1.80 g (92%), was isolated by
3 column chromatography (0-1.5% EtOAc-hexanes) as a colorless oil.
4 ¹H NMR (CDCl₃) δ: 7.38 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 2.9 Hz), 6.56
5 (1H, dd, J = 2.9, 8.5 Hz), 1.47 (9H, s), 1.29-1.24 (3H, m), 1.09 (18H, d, J =
6 6.7 Hz).

7 Ethyl 2-*tert*-butyl-4-triisopropylsilanyloxy-benzoate (**Intermediate 106**)

8 To a solution of (4-bromo-3-*tert*-butyl-phenoxy)-triisopropyl-silane
9 (**Intermediate 105**, 1.00 g, 2.60 mmols) in 15 mL Et₂O cooled to -78 °C
10 was added 3.6 mL of *tert*-butyllithium, 1.7 M in pentane (395.0 mg, 6.2
11 mmols). After stirring for 30 minutes ethyl chloroformate (607.6 mg, 5.6
12 mmols) was added. The resulting solution was warmed to room temperature
13 and quenched by the addition of saturated aqueous NH₄Cl. The mixture was
14 extracted with EtOAc and the combined organic layers dried (MgSO₄)
15 concentrated under reduced pressure. The residue was chromatographed (2-
16 5% EtOAc-hexanes) to give 1.23 g (88%) of the title compound as a
17 colorless oil.

18 ¹H NMR (CDCl₃) δ: 7.24 (1H, d, J = 8.2 Hz), 6.97 (1H, d, J = 2.6 Hz), 6.69
19 (1H, dd, J = 2.6, 8.2 Hz), 4.33 (2H, q, J = 7.1 Hz), 1.39 (9H, s), 1.37 (3H, t,
20 J = 7.1 Hz), 1.29-1.21 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

21 [4-(1-Ethoxyvinyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane (**Intermediate**
22 **107**)

23 Using General Procedure 1; ethyl 2-*tert*-butyl-4-
24 triisopropylsilanyloxy-benzoate (**Intermediate 106**, 1.30 g, 3.44 mmols)
25 and 7.2 mL of Tebbe's Reagent (1.03 g, 3.61 mmols) were reacted. The
26 reaction required 7 days at room temperature to go to completion. The
27 standard work-up afforded 1.29 g (78%) of the title compound after column

1 chromatography (1-2% EtOAc-hexanes).

2 ¹H NMR (CDCl₃) δ: 7.05 (1H, d, J = 8.2 Hz), 6.94 (1H, d, J = 2.6 Hz), 6.63
3 (1H, dd, J = 2.6, 8.2 Hz), 4.20 (1H, d, J = 1.7 Hz), 4.08 (1H, d, J = 1.7 Hz),
4 3.83 (2H, q, J = 7.1 Hz), 1.37 (9H, s), 1.36 (3H, t, J = 7.1 Hz), 1.27-1.20
5 (3H, m), 1.10 (18H, d, J = 6.7 Hz).

6 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-triisopropyl-silane

7 (**Intermediate 108**)

8 Using General Procedure 2; [4-(1-ethoxyvinyl)-3-*tert*-butyl-
9 phenoxy]-triisopropyl-silane (**Intermediate 107**, 320.0 mg, 0.85 mmols),
10 Et₂Zn (325.0 mg, 2.63 mmols), and CH₂I₂ (704.0 mg, 2.63 mmols) in 5.0
11 mL Et₂O afforded 257.0 mg (66%) of the title compound as a colorless oil
12 after chromatography (1-2.5% EtOAc - hexanes).

13 ¹H NMR (CDCl₃) δ: 7.24 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2.6 Hz), 6.60
14 (1H, dd, J = 2.6, 8.5 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.50 (9H, s), 1.29-1.21
15 (3H, m), 1.11 (18H, d, J = 6.7 Hz), 1.04 (3H, t, J = 7.1 Hz).

16 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenol (**Intermediate 109**)

17 To a solution of [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenoxy]-
18 triisopropyl-silane (**Intermediate 108**, 600.0 mg, 1.54 mmol) in 3 mL THF
19 at 0 °C was added tetrabutylammonium fluoride (802.8.0 mg, 3.07 mmols;
20 3.1 mL of a 1 M solution in THF). The solution was stirred at 0 °C for 30
21 minutes and then quenched by the addition of H₂O. The mixture was
22 extracted with EtOAc and the combined organic layers were washed with
23 H₂O and saturated aqueous NaCl before being dried (MgSO₄) and
24 concentrated under reduced pressure. The title compound (400 mg, 88%)
25 was isolated from the residue by column chromatography (4-10% EtOAc-
26 hexanes) as a colorless solid.

27 ¹H NMR (CDCl₃) δ: 7.29 (1H, d, J = 8.2 Hz), 7.01 (1H, d, J = 2.6 Hz), 6.57

1 (1H, dd, J = 2.6, 8.2 Hz), 3.29 (2H, q, J = 7.1 Hz), 1.59 (9H, s), 1.08-1.04
2 (7H, m).
3 4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenyl 1,1,1-trifluoromethansulfonate
4 **(Intermediate 110)**

5 A solution of 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenol
6 **(Intermediate 109**, 400.0 mg, 1.71 mmol) in 10 mL of CH₂Cl₂ was cooled
7 to 0 °C and to it was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-
8 chloropyridine (705.0 mg, 1.79 mmol) and triethylamine (522.0 mg, 5.1
9 mmols). The resulting solution was warmed to room temperature and stirred
10 overnight. The reaction was quenched by the addition of H₂O and the
11 mixture extracted with EtOAc and the combined organic layers were washed
12 with 10% aqueous HCl, saturated aqueous NaHCO₃, H₂O, and saturated
13 aqueous NaCl. The solution was dried (MgSO₄) and concentrated under
14 reduced pressure. The title compound was isolated by column
15 chromatography (2-4% EtOAc-hexanes) as a colorless oil, 542.0 mg (87%).
16 ¹H NMR (CDCl₃) δ: 7.48 (1H, d, J = 8.5 Hz), 7.39 (1H, d, J = 2.6 Hz), 7.01
17 (1H, dd, J = 2.6, 8.5 Hz), 3.26 (2H, q, J = 7.1 Hz), 1.52 (9H, s), 1.12 (2H,
18 bs), 1.08-1.04 (5H, m).
19 [4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-trimethylsilane
20 **(Intermediate 111)**

21 Using General Procedure D; 4-(1-ethoxycyclopropyl)-3-*tert*-butyl-
22 phenyl 1,1,1-trifluoromethansulfonate **(Intermediate 110**, 260.0 mg, 0.71
23 mmol) in triethylamine (4 mL) and DMF (6 mL) was sparged with argon for
24 5 minutes. Trimethylsilylacetylene (0.70 g, 7.1 mmols) was then added
25 followed by dichlorobis-(triphenylphosphine)palladium(II) (40.0 mg, 0.06
26 mmol). The resulting reaction mixture was heated to 95 °C for 18 hours.
27 The title compound, 215.0 mg (96%), was isolated by chromatography (0 -

1 2% EtOAc - hexanes) as an orange oil.

2 ¹H NMR (CDCl₃) δ: 7.63 (1H, d, J = 1.7 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.19

3 (1H, dd, J = 1.7, 7.9 Hz), 3.24 (2H, q, J = 7.1 Hz), 1.51 (9H, s), 1.10 (2H,

4 bs), 1.06-1.01 (5H, m), 0.25 (9H, s).

5 1-(1-Ethoxycyclopropyl)-4-ethynyl-2-*tert*-butylbenzene (Intermediate 112)

6 Using General Procedure E; [4-(1-ethoxycyclopropyl)-3-*tert*-butyl-
7 phenylethynyl]-trimethylsilane (Intermediate 111, 215.0 mg, 0.69 mmol) in

8 methanol (10 mL) was treated with potassium carbonate (80.0 mg, 0.58

9 mmol) and stirred overnight at ambient temperature. The crude alkyne, 169

10 mg, was used directly in the next reaction.

11 ¹H NMR (CDCl₃) δ: 7.68 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.23

12 (1H, dd, J = 1.8, 7.9 Hz), 3.26 (2H, q, J = 7.1 Hz), 3.06 (1H, s), 1.51 (9H, s),

13 1.11 (2H, bs), 1.07-1.02 (5H, m).

14 Ethyl 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate

15 (Compound 103, General Formula 2)

16 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-

17 *tert*-butylbenzene (Intermediate 112, 70.0 mg, 0.30 mmol) and ethyl-4-iodo

18 benzoate (Reagent A, 85.0 mg, 0.30 mmol) in triethylamine (5 mL) was

19 treated with copper(I)iodide (19.0 mg, 0.01 mmol) and sparged with argon

20 for 5 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (70 mg, 0.01

21 mmol) was added and the reaction mixture was stirred overnight at room

22 temperature. Column chromatography (1-2% EtOAc - hexanes) afforded

23 70.0 mg (73%) of the title compound.

24 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 1.7 Hz), 7.59

25 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.28 (1H, dd, J = 1.7, 7.9 Hz),

26 4.39 (2H, q, J = 7.1 Hz), 3.28 (2H, q, J = 7.1 Hz), 1.55 (9H, s), 1.40 (3H, t,

27 J = 7.1 Hz), 1.12 (2H, bs), 1.08-1.04 (5H, m).

1 Methyl {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-
2 acetate (Compound 104, General Formula 2)

3 Using General Procedure F; 1-(1-ethoxycyclopropyl)-4-ethynyl-2-
4 *tert*-butylbenzene (**Intermediate 112**, 95.0 mg, 0.39 mmol) and methyl-(4-
5 iodophenyl)-acetate (**Reagent B**, 108.0 mg, 0.39 mmol) in triethylamine (8
6 mL) was treated with copper(I)iodide (25.0 mg, 0.13 mmol) and sparged
7 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (91
8 mg, 0.13 mmol) was added and the reaction mixture was stirred overnight at
9 room temperature. Column chromatography (2-5% EtOAc - hexanes)
10 afforded 100.0 mg (72%) of the title compound.

11 ¹H NMR (CDCl₃) δ: 7.70 (1H, d, J = 1.5 Hz), 7.50 (2H, d, J = 7.9 Hz), 7.38
12 (1H, d, J = 7.9 Hz), 7.27 (3H, m), 3.70 (3H, s), 3.64 (2H, s), 3.28 (2H, q, J =
13 7.1 Hz), 1.54 (9H, s), 1.12 (2H, bs), 1.08-1.03 (5H, m).

14 4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoic acid
15 (Compound 105, General Formula 2)

16 Using General Procedure I; a solution of ethyl 4-[4-(1-
17 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-benzoate (**Compound 103**,
18 70.0 mg, 0.18 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
19 treated with NaOH (240.0 mg, 6.0 mmols, 3.0 mL of a 2N aqueous solution)
20 and stirred overnight at room temperature. Work-up afforded 40 mg (62%)
21 the title compound as a pale-yellow solid.

22 ¹H NMR (d₆-acetone) δ: 8.06 (2H, d, J = 8.7 Hz), 7.76 (1H, d, J = 1.8 Hz),
23 7.67 (2H, d, J = 8.7 Hz), 7.50 (1H, d, J = 7.9 Hz), 7.33 (1H, dd, J = 1.8, 7.9
24 Hz), 3.28 (2H, q, J = 7.3 Hz), 1.54 (9H, s), 1.13 (2H, bs), 1.10 (2H, m), 1.02
25 (3H, t, J = 7.3 Hz).

26 {4-[4-(1-Ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic
27 acid (Compound 106, General Formula 2)

1 Using General Procedure I; a solution of methyl {4-[4-(1-
2 ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetate
3 (**Compound 104**, 100.0 mg, 0.26 mmol) in ethanol (4 mL) and
4 tetrahydrofuran (4 mL) was treated with NaOH (240.0 mg, 6.0 mmols, 3.0
5 mL of a 2N aqueous solution) and stirred at 50 °C for 4h. Work-up and
6 isolation by HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded 70.0 mg
7 (73%) of the title compound.

8 ¹H NMR (CDCl₃) δ: 7.73 (1H, d, J = 1.3 Hz), 7.53 (2H, d, J = 7.9 Hz), 7.41
9 (1H, d, J = 7.9 Hz), 7.28 (3H, m), 3.69 (2H, s), 3.31 (2H, q, J = 7.1 Hz),
10 1.56 (9H, s), 1.15 (2H, bs), 1.11-1.05 (5H, m).

11 1-(4-Bromophenyl)-cyclopropanecarbonitrile (Intermediate 113)

12 To a 50% aqueous NaOH solution (40.0 g, wt/wt) was added benzyl
13 triethylammonium chloride (1.0 g, 4.4 mmols), 4-bromobenzonitrile (19.6 g,
14 0.10 mol), and 1,2-dibromoethane (56.4 g, 0.30 mol). The mixture was
15 stirred overnight at room temperature and then diluted with 100 mL of H₂O.
16 This mixture was extracted with EtOAc and the combined extracts were
17 washed with saturated aqueous NaHS₂O₃, H₂O, and saturated aqueous NaCl
18 before being dried (MgSO₄) and concentrated under reduced pressure.
19 Bulb-to-bulb distillation afforded 18.8 g (85%) of the title compound as a
20 colorless solid.

21 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 8.6 Hz), 1.75
22 (2H, dd, J = 5.2, 7.6 Hz), 1.39 (2H, dd, J = 5.2, 7.6 Hz).

23 1-(4-Bromophenyl)-cyclopropanecarboxylic acid (Intermediate 114)

24 To a solution of KOH (6.06 g, 0.11 mol) in 10 mL of H₂O was added
25 40 mL of ethylene glycol and 1-(4-bromophenyl)-cyclopropanecarbonitrile
26 (**Intermediate 113**, 10.0 g, 0.45 mol). This solution was heated to 135-140
27 °C for 4h, cooled to room temperature, and then poured into a mixture of

1 100 mL ice and 10% aqueous HCl. The resulting mixture was allowed to
2 stand overnight at 5 °C, the solid was collected by filtration and washed
3 with H₂O. The colorless solid was dried under reduced pressure to give
4 10.6 g (97%) of the title compound.
5 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 1.68
6 (2H, dd, J = 4.0, 7.1 Hz), 1.24 (2H, dd, J = 4.0, 7.1 Hz).
7 *Tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-carbamate (Intermediate 115)
8 A solution of 1-(4-bromophenyl)-cyclopropanecarboxylic acid
9 (Intermediate 114, 2.32 g, 9.62 mmols), diphenylphosphoryl azide (2.65 g,
10 9.62 mmols), triethylamine (973.0 mg, 9.62 mmols) in 40 mL *tert*-BuOH
11 (distilled from Na⁺) was heated to reflux for 17h. The solution was
12 concentrated under reduced pressure and the residue dissolved in EtOAc
13 and washed with 5% aqueous HCl, H₂O, saturated aqueous NaHCO₃, and
14 saturated aqueous NaCl before being dried over MgSO₄. Concentration of
15 the dry solution under reduced pressure and column chromatography (5-
16 10% EtOAc - hexanes) afforded 2.01 g (67%) of the title compound as a
17 colorless solid.
18 ¹H NMR (CDCl₃) δ: 7.39 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 5.35
19 (1H, bs), 1.43 (9H, s), 1.26 (2H, m), 1.17 (2H, m).
20 1-(4-Bromophenyl)-cyclopropylamine (Intermediate 116)
21 To a solution of *tert*-butyl [1-(4-bromophenyl)-cyclopropyl]-
22 carbamate (Intermediate 115, 1.08 g, 3.40 mmols) in 20 mL MeOH and 20
23 mL THF was added 20 mL of 3M aqueous HCl. The solution was warmed
24 to 35 °C for 3 hours and then stirred for 17h at 25 °C. The reaction was
25 quenched by adjusting the pH of the solution to 12 with 3M aqueous NaOH.
26 The mixture was extracted with Et₂O and the combined organic layers were
27 washed with H₂O and saturated aqueous NaCl before being dried (MgSO₄)

1 and concentrated under reduced pressure. The title compound 613 mg
2 (85%) was used without further purification.
3 ¹H NMR (CDCl₃) δ: 7.43 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 1.89
4 (2H, bs), 1.07 (2H, m), 0.95 (2H, m).
5 *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide (Intermediate 117)
6 To a solution of 1-(4-bromophenyl)-cyclopropylamine (Intermediate
7 116, 84 mg, 0.4 mmol) in 4 mL CH₂Cl₂ at room temperature was added
8 propionyl chloride (43.0 mg, 0.47 mmol) and pyridine (56.0 mg, 0.71
9 mmol). After stirring 17 hours at room temperature the reaction was
10 quenched by the addition of H₂O and extracted with EtOAc. The combined
11 extracts were washed with 10% aqueous HCl, saturated aqueous NaHCO₃,
12 and saturated aqueous NaCl before being dried (MgSO₄) and concentrated
13 under reduced pressure. The title compound 85.0 mg (67%), was isolated
14 by column chromatography (20-50% EtOAc-hexanes) as a colorless solid.
15 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 6.40
16 (1H, s), 2.19 (2H, q, J = 7.2 Hz), 1.18-1.24 (4H, m), 1.12 (3H, t, J = 7.2 Hz).
17 [1-(4-Bromophenyl)-cyclopropyl]-propylamine (Intermediate 118)
18 To a solution of *N*-[1-(4-bromophenyl)-cyclopropyl]-propionamide
19 (Intermediate 117, 85.0 mg, 0.32 mmol) in THF (5 mL) at 0 °C was added
20 BH₃-Me₂S (48.0 mg, 0.63 mmol; 0.31 mL of a 2M solution in THF). The
21 solution was heated to 55 °C for 17 hours, cooled to room temperature,
22 saturated aqueous NaHCO₃ was added and the resulting mixture was stirred
23 for 2 hours. This mixture was extracted with EtOAc and the combined
24 organic layers were washed with H₂O and saturated aqueous NaCl before
25 being dried (MgSO₄) and concentrated under reduced pressure. The title
26 compound was isolated by column chromatography (10-30% EtOAc-
27 hexanes).

1 ¹H NMR (CDCl₃) δ: 7.42 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 2.46
2 (2H, t, J = 7.3 Hz), 1.40 (2H, m), 0.98 (2H, m), 0.86 (5H, m).

3 Propyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine

4 **(Intermediate 119)**

5 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-
6 propylamine (**Intermediate 118**, 100.0 mg, 0.39 mmol) in triethylamine (8
7 mL) was treated with copper(I)iodide (13.0 mg, 0.06 mmol) and then
8 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1
9 mmols) was then added followed by
10 dichlorobis(triphenylphosphine)palladium(II) (48.0 mg, 0.06 mmol). The
11 resulting reaction mixture was heated to 70 °C for 5 days. The title
12 compound (80.0 mg, 75%) was isolated by chromatography (0 - 10% EtOAc
13 - hexanes) as an orange oil.

14 ¹H NMR (CDCl₃) δ: 7.41 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 2.45
15 (2H, t, J = 7.3 Hz), 1.39 (2H, m), 0.98 (2H, m), 0.87 (2H, m), 0.84 (3H, t, J
16 = 7.3 Hz), 0.24 (9H, s).

17 [1-(4-Ethynylphenyl)-cyclopropyl]-propylamine (**Intermediate 120**)

18 Using General Procedure E; propyl-[1-(4-trimethylsilanylethynyl)-
19 phenyl]-cyclopropyl]-amine (**Intermediate 119**, 80.0 mg, 0.30 mmols) in
20 methanol (8 mL) was treated with potassium carbonate (80.0 mg, 0.59
21 mmol) and stirred overnight at ambient temperature. The crude alkyne (58
22 mg, 100%) was used directly in the next reaction.

23 ¹H NMR (CDCl₃) δ: 7.44 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 3.05
24 (1H, s), 2.46 (2H, t, J = 7.3 Hz), 1.41 (2H, m), 1.00 (2H, m), 0.90 (2H, m),
25 0.86 (3H, t, J = 7.3 Hz).

26 Ethyl 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-benzoate

27 **(Compound 107, General Formula 2)**

1 Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-
2 propylamine (**Intermediate 120**, 38.0 mg, 0.19 mmol) and ethyl-4-iodo
3 benzoate (**Reagent A**, 58.0 mg, 0.21 mmol) in triethyl amine (6 mL) was
4 treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with argon
5 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04
6 mmol) was added and the reaction mixture was stirred overnight at room
7 temperature. Column chromatography (5-15% EtOAc - hexanes) afforded
8 40.0 mg (61%) of the title compound as an orange oil.
9 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.49
10 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.49
11 (2H, t, J = 7.3 Hz), 1.46 (2H, m), 1.41 (3H, t, J = 7.1 Hz), 1.01 (2H, m), 0.89
12 (2H, m), 0.87 (3H, t, J = 7.3 Hz).

13 4-[4-(1-Propylamino-cyclopropyl)-phenylethynyl]-benzoic acid
14 (**Compound 108, General Formula 2**)

15 Using General Procedure I; a solution of ethyl 4-[4-(1-propylamino-
16 cyclopropyl)-phenylethynyl]-benzoate (**Compound 107**, 40.0 mg, 0.12
17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
18 NaOH (160.0 mg, 4.0 mmols, 2.0 mL of a 2N aqueous solution) and stirred
19 overnight at room temperature. Work-up afforded 25.0 mg (69%) of the
20 title compound as a solid.

21 ¹H NMR (d₆-DMSO) δ: 7.97 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz),
22 7.50 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 2.39 (2H, t, J = 7.3 Hz),
23 1.37 (2H, m), 1.00 (2H, m), 0.93 (2H, m), 0.84 (3H, t, J = 7.3 Hz).

24 [1-(4-Bromophenyl)-cyclopropyl]-dipropylamine (**Intermediate 121**)

25 To a solution of 1-(4-bromophenyl)-cyclopropylamine (**Intermediate**
26 **116**) in CH₃CN / HOAc (5 mL, 9:1, v/v) and THF 3 mL at 0 °C was added
27 propionaldehyde (277.0 mg, 4.95 mmols) and NaCNBH₃ (153.0 mg, 2.47

1 mmols). The reaction was warmed to room temperature and after 5 hours
2 quenched with H₂O. The pH of the solution was adjusted to 8-9 using
3 aqueous NaOH and extracted with EtOAc. The combined extracts were
4 washed with H₂O and saturated aqueous NaCl, dried (MgSO₄) and
5 concentrated under reduced pressure. The title compound, 190.0 mg (56%),
6 was isolated by column chromatography (2-5% EtOAc-hexanes).
7 ¹H NMR (CDCl₃) δ: 7.42 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 2.39
8 (4H, t, J = 7.3 Hz), 1.62-1.40 (4H, m), 0.96 (2H, m), 0.86 (6H, t, J = 7.3
9 Hz), 0.80 (2H, m).

10 Dipropyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
11 **(Intermediate 122)**

12 Using General Procedure D; [1-(4-bromophenyl)-cyclopropyl]-
13 dipropylamine (**Intermediate 121**, 150.0 mg, 0.50 mmol) in triethylamine
14 (5 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol) and then
15 sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 7.1
16 mmols) was then added followed by
17 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The
18 resulting reaction mixture was heated to 70 °C for 5d. The title compound
19 was isolated by chromatography (0 - 3% EtOAc - hexanes).
20 ¹H NMR (CDCl₃) δ: 7.35 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 2.39
21 (4H, t, J = 7.3 Hz), 1.55-1.42 (4H, m), 0.96 (2H, m), 0.88-0.79 (8H, m), 0.25
22 (9H, s).

23 [1-(4-Ethynylphenyl)-cyclopropyl]-dipropylamine (Intermediate 123)

24 Using General Procedure E; dipropyl-[1-(4-trimethylsilanylethynyl-
25 phenyl)-cyclopropyl]-amine (**Intermediate 122**, 45.0 mg, 0.14 mmols) in
26 methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37
27 mmol) and stirred overnight at ambient temperature. The crude alkyne (34

1 mg, 100%) was used directly in the next reaction.

2 ¹H NMR (CDCl₃) δ: 7.42 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz),
3 2.40(4H, t, J = 7.3 Hz), 1.53-1.40 (4H, m), 0.96 (2H, m), 0.90-0.79 (8H, m).

4 Ethyl 4-[4-(1-dipropylamino-cyclopropyl)-phenylethynyl]-benzoate

5 **(Compound 109, General Formula 2)**

6 Using General Procedure F; [1-(4-ethynylphenyl)-cyclopropyl]-
7 dipropylamine (**Intermediate 123**, 34.0 mg, 0.16 mmol) and ethyl-4-iodo
8 benzoate (**Reagent A**, 59.0 mg, 0.21 mmol) in triethyl amine (6 mL) was
9 treated with copper(I)iodide (13.0 mg, 0.07 mmol) and sparged with argon
10 for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (49 mg, 0.07
11 mmol) was added and the reaction mixture was stirred overnight at room
12 temperature. Column chromatography (2-4% EtOAc - hexanes) afforded
13 the title compound as a yellow oil.

14 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.49
15 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.43
16 (4H, t, J = 7.3 Hz), 1.52-1.42 (4H, m), 1.41 (3H, t, J = 7.1 Hz), 0.99 (2H,
17 m), 0.88-0.83 (8H, m).

18 4-[4-(1-Dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid

19 **(Compound 110, General Formula 2)**

20 Using General Procedure I; a solution of ethyl 4-[4-(1-
21 dipropylamino-cyclopropyl)-phenylethynyl]-benzoate (**Compound 109**,
22 51.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
23 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
24 and stirred overnight at room temperature. Work-up afforded 32.0 mg
25 (70%) of the title compound as a colorless solid.

26 ¹H NMR (d₆-DMSO) δ: 7.98 (2H, d, J = 8.3 Hz), 7.67 (6H, m), 3.05-2.89
27 (4H, m), 1.98 (2H, m), 1.72 (4H, m), 1.23 (2H, m), 0.88 (6H, t, J = 7.3 Hz).

1 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (Intermediate 124) and

2 Dibenzyl-[1-(4-bromophenyl)-cyclopropyl]-amine (Intermediate 125)

3 A solution of 1-(4-bromophenyl)-cyclopropylamine (Intermediate
4 116, 244.0 mg, 1.15 mmols) and benzyl bromide (255.0 mg, 1.50 mmols) in
5 4 mL DMF was stirred at 85 °C for 6 hours, cooled to room temperature and
6 stirred overnight. The solution was diluted with H₂O and the pH adjusted to
7 8-9 with aqueous NaOH. The solution was extracted with EtOAc and the
8 combined organic layers were washed with H₂O and saturated aqueous
9 NaCl, dried (MgSO₄) and concentrated under reduced pressure. Column
10 chromatography (5-10% EtOAc-Hexanes) afforded 110 mg (32%) of the *N*-
11 benzyl amine.

12 ¹H NMR (CDCl₃) δ: 7.48 (2H, d, J = 8.4 Hz), 7.30-7.23 (7H, m), 3.68 (2H,
13 s), 1.07 (2H, m), 0.93 (2H, m); and 100 mg (22%) of the *N,N*-dibenzyl
14 amine, ¹H NMR (CDCl₃) δ: 7.55 (2H, d, J = 8.3 Hz), 7.40-7.19 (12H, m),
15 3.61 (4H, s), 0.87 (2H, m), 0.71 (2H, m).

16 Benzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
17 (Intermediate 126)

18 Using General Procedure D; benzyl-[1-(4-bromophenyl)-
19 cyclopropyl]-amine (Intermediate 124, 110.0 mg, 0.36 mmol) in
20 triethylamine (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol)
21 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g,
22 7.1 mmols) was then added followed by
23 dichlorobis(triphenylphosphine)palladium(II) (38.0 mg, 0.05 mmol). The
24 resulting reaction mixture was heated to 70 °C for 5d. The title compound
25 85 mg (74%) was isolated by chromatography (1 - 10% EtOAc - hexanes).
26 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.3 Hz), 7.31-7.22 (7H, m), 3.67 (2H,
27 s), 1.06 (2H, m), 0.94 (2H, m), 0.26 (9H, s).

1 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (Intermediate 127)

2 Using General Procedure E; benzyl-[1-(4-trimethylsilylethynyl-
3 phenyl)-cyclopropyl]-amine (**Intermediate 126**, 85.0 mg, 0.27 mmol) in
4 methanol (5 mL) was treated with potassium carbonate (50.0 mg, 0.37
5 mmol) and stirred overnight at ambient temperature. The crude alkyne (65
6 mg, 100%) was used directly in the next reaction.

7 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.23
8 (5H, m), 3.68 (2H, s), 3.08 (1H, s), 1.07 (2H, m), 0.95 (2H, m).

9 Ethyl 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoate

10 (**Compound 111, General Formula 2**)

11 Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-
12 cyclopropyl]-amine (**Intermediate 127**, 65.0 mg, 0.27 mmol) and ethyl-4-
13 iodo benzoate (**Reagent A**, 68.0 mg, 0.27 mmol) in triethyl amine (8 mL)
14 was treated with copper(I)iodide (16.0 mg, 0.08 mmol) and sparged with
15 argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (58 mg,
16 0.08 mmol) was added and the reaction mixture was stirred overnight at
17 room temperature. Column chromatography (2-5% EtOAc - hexanes)
18 afforded 90 mg (90%) of the title compound as an orange solid.

19 ¹H NMR (CDCl₃) δ: 8.05 (2H, d, J = 8.3 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.55
20 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.32-7.22 (5H, m), 4.40 (2H, q,
21 J = 7.1 Hz), 3.72 (2H, s), 1.42 (2H, t, J = 7.1 Hz), 1.01 (2H, m), 0.99 (2H,
22 m).

23 4-[4-(1-Benzylamino-cyclopropyl)-phenylethynyl]-benzoic acid

24 (**Compound 112, General Formula 2**)

25 Using General Procedure I; a solution of ethyl 4-[4-(1-benzylamino-
26 cyclopropyl)-phenylethynyl]-benzoate (**Compound 111**, 75.0 mg, 0.19
27 mmol) in ethanol (4 mL) and tetrahydrofuran (4 mL) was treated with

- 1 NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and stirred
2 overnight at room temperature. Work-up afforded 35.0 mg (50%) of the
3 title compound as a colorless solid.
4 ¹H NMR (CD₃OD) δ: 7.93 (2H, d, J = 8.3 Hz), 7.61-7.51 (6H, m), 7.32-7.23
5 (5H, m), 3.98 (2H, s), 1.33(2H, m), 1.19 (2H, m).
6 Dibenzyl-[1-(4-trimethylsilanylethynyl-phenyl)-cyclopropyl]-amine
7 **(Intermediate 128)**
8 Using General Procedure D; dibenzyl-[1-(4-bromophenyl)-
9 cyclopropyl]-amine (**Intermediate 125**, 45.0 mg, 0.11 mmol) in
10 triethylamine (8 mL) was treated with copper(I)iodide (10.0 mg, 0.05 mmol)
11 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.35 g,
12 3.6 mmols) was then added followed by
13 dichlorobis(triphenylphosphine)palladium(II) (35.0 mg, 0.05 mmol). The
14 resulting reaction mixture was heated to 70 °C for 5d. The title compound
15 40 mg (88%) was isolated by chromatography (hexanes).
16 ¹H NMR (CDCl₃) δ: 7.52 (2H, d, J = 8.3 Hz), 7.36-7.24 (12H, m), 3.60 (4H,
17 s), 0.87 (2H, m), 0.67 (2H, m), 0.29 (9H, s).
18 Dibenzyl-[1-(4-ethynylphenyl)-cyclopropyl]-amine (**Intermediate 129**)
19 Using General Procedure E; dibenzyl-[1-(4-trimethylsilanylethynyl-
20 phenyl)-cyclopropyl]-amine (**Intermediate 128**, 100.0 mg, 0.26 mmol) in
21 methanol (5 mL) was treated with potassium carbonate (60.0 mg, 0.44
22 mmol) and stirred overnight at ambient temperature. The crude alkyne (80
23 mg, 99%) was used directly in the next reaction.
24 ¹H NMR (CDCl₃) δ: 7.53 (2H, d, J = 7.9 Hz), 7.36 (2H, d, J = 7.9 Hz), 7.28-
25 7.25 (10H, m), 3.62 (4H, s), 3.11 (1H, s), 0.88 (2H, m), 0.68 (2H, m).
26 Ethyl 4-[4-(1-dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate
27 **(Compound 113, General Formula 2)**

1 Using General Procedure F; dibenzyl-[1-(4-ethynylphenyl)-
2 cyclopropyl]-amine (**Intermediate 129**, 40.0 mg, 0.12 mmol) and ethyl-4-
3 iodo benzoate (**Reagent A**, 60.0 mg, 0.22 mmol) in triethylamine (5 mL)
4 was treated with copper(I)iodide (8.0 mg, 0.04 mmol) and sparged with
5 argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II) (27 mg,
6 0.04 mmol) was added and the reaction mixture was stirred overnight at
7 room temperature. Column chromatography (2-5% EtOAc - hexanes)
8 afforded the title compound as an oil.
9 ¹H NMR (CDCl₃) δ: 8.04 (2H, d, J = 8.5 Hz), 7.79 (4H, m), 7.42 (2H, d, J =
10 7.9 Hz), 7.29-7.17 (10H, m), 4.40 (2H, q, J = 7.1 Hz), 3.63 (4H, s), 1.42
11 (3H, t, J = 7.1 Hz), 0.88 (2H, m), 0.73 (2H, m).
12 4-[4-(1-Dibenzylamino-cyclopropyl)-phenylethynyl]-benzoic acid
13 (**Compound 114, Formula 2**)

14 Using General Procedure I; a solution of ethyl 4-[4-(1-
15 dibenzylamino-cyclopropyl)-phenylethynyl]-benzoate (**Compound 113**,
16 48.0 mg, 0.10 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was
17 treated with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution)
18 and stirred overnight at room temperature. Work-up afforded 42.0 mg
19 (93%) of the title compound as a colorless solid.
20 ¹H NMR (d₆-DMSO) δ: 7.98 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz),
21 7.64 (2H, d, J = 7.9 Hz), 7.47 (2H, d, J = 7.9 Hz), 7.28-7.20 (10H, m), 3.57
22 (4H, s), 0.84 (2H, m), 0.69 (2H, m).

23 Benzyl-[1-(4-bromophenyl)-cyclopropyl]-methylamine (**Intermediate 130**)

24 To a solution of benzyl-[1-(4-bromophenyl)-cyclopropyl]-amine
25 (**Intermediate 124**, 100.0 mg, 0.33 mmol) in 5 mL of acetone was added
26 K₂CO₃ (91 mg, 0.66 mmol) and iodomethane (2.28 g, 16.1 mmols). The
27 resulting mixture was stirred at 25 °C for 20 hours, diluted with Et₂O, and

1 washed with H₂O and saturated aqueous NaCl. The solution was dried
2 (MgSO₄) and concentrated under reduced pressure to give 90 mg (86%) of
3 the title compound.

4 ¹H NMR (CDCl₃) δ: 7.47 (2H, d, J = 8.5 Hz), 7.29-7.18 (7H, m), 3.53 (2H,
5 s), 2.07 (3H, s), 1.07 (2H, m), 0.86 (2H, m).

6 Benzyl-[1-(4-trimethylsilyl-ethynyl-phenyl)-cyclopropyl]-methylamine
7 (**Intermediate 131**)

8 Using General Procedure D; benzyl-[1-(4-bromophenyl)-
9 cyclopropyl]-methylamine (**Intermediate 130**, 90.0 mg, 0.28 mmol) in
10 triethylamine (8 mL) was treated with copper(I)iodide (6.0 mg, 0.03 mmol)
11 and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g,
12 7.1 mmols) was then added followed by
13 dichlorobis(triphenylphosphine)palladium(II) (20.0 mg, 0.03 mmol). The
14 resulting reaction mixture was heated to 70 °C for 5 days. The title
15 compound 80 mg (84%) was isolated by chromatography (0-2% EtOAc-
16 hexanes).

17 ¹H NMR (CDCl₃) δ: 7.46 (2H, d, J = 8.2 Hz), 7.32-7.18 (7H, m), 3.52 (2H,
18 s), 2.06 (3H, s), 1.06 (2H, m), 0.87(2H, m), 0.26 (9H, s).

19 Benzyl-[1-(4-ethynylphenyl)-cyclopropyl]-methylamine (**Intermediate**
20 **132**)

21 Using General Procedure E; benzyl-[1-(4-trimethylsilyl-ethynyl-
22 phenyl)-cyclopropyl]-methylamine (**Intermediate 131**, 80.0 mg, 0.24 mmol)
23 in methanol (5 mL) was treated with potassium carbonate (80.0 mg, 0.59
24 mmol) and stirred overnight at ambient temperature. The crude alkyne (60
25 mg, 99%) was used directly in the next reaction.

26 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.33-7.21 (7H, m), 3.55 (2H,
27 s), 3.08 (1H, s), 2.08 (3H, s), 1.07 (2H, m), 0.89 (2H, m).

1 Ethyl 4-{4-[1-(benzyl-methylamino)-cyclopropyl]-phenylethynyl}-benzoate

2 **(Compound 115, General Formula 2)**

3 Using General Procedure F; benzyl-[1-(4-ethynylphenyl)-
4 cyclopropyl]-methylamine (**Intermediate 132**, 70.0 mg, 0.28 mmol) and
5 ethyl-4-iodo benzoate (**Reagent A**, 77.0 mg, 0.28 mmol) in triethylamine (5
6 mL) was treated with copper(I)iodide (18.0 mg, 0.10 mmol) and sparged
7 with argon for 5 minutes. Dichlorobis (triphenylphosphine)palladium(II)
8 (65 mg, 0.10 mmol) was added and the reaction mixture was stirred
9 overnight at room temperature. Column chromatography (2-5% EtOAc -
10 hexanes) afforded 86 mg (75%) of the title compound as an oil.

11 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.53
12 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.39 (2H, q, J =
13 7.1 Hz), 3.57 (2H, s), 2.10 (3H, s), 1.41 (3H, t, J = 7.1 Hz), 1.10 (2H, m),
14 0.92 (2H, m).

15 4-[4-(1-Benzylmethylamino-cyclopropyl)-phenylethynyl]-benzoic acid

16 **(Compound 116, General Formula 2)**

17 Using General Procedure I; a solution of ethyl 4-{4-[1-(benzyl-
18 methylamino)-cyclopropyl]-phenylethynyl}-benzoate (**Compound 115**, 65.0
19 mg, 0.16 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated
20 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and
21 stirred overnight at room temperature. Work-up afforded 45.0 mg (75%) of
22 the title compound as a solid.

23 ¹H NMR (d₆-DMSO) δ: 7.96 (2H, d, J = 8.3 Hz), 7.66 (2H, d, J = 8.3 Hz),
24 7.58 (2H, d, J = 8.2 Hz), 7.42 (2H, d, J = 8.2 Hz), 7.29-7.18 (5H, m), 3.52
25 (2H, s), 2.00 (3H, s), 1.02 (2H, m), 0.87 (2H, m).

26 (4-Bromo-2-methyl-phenyl)-methanol (**Intermediate 133**)

27 A solution of methyl 4-bromo-2-methyl-benzoate (1.05 g, 4.58

1 mmols) in 10 mL of Et₂O was cooled to 0 °C and treated with LiAlH₄
2 (177.0 mg, 4.58 mmols), stirred for 3 hours, and then carefully quenched
3 with H₂O. The mixture was extracted with Et₂O and the combined organic
4 layers were washed with H₂O and saturated aqueous NaCl, dried (MgSO₄),
5 and concentrated under reduced pressure. The title compound, 830.0 mg
6 (90%), was isolated by column chromatography (10-30% EtOAc-hexanes)
7 as a colorless oil.

8 ¹H NMR (CDCl₃) δ: 7.30 (2H, m), 7.18 (1H, d, J = 8.8 Hz), 4.57 (2H, d, J =
9 5.5 Hz), 2.27 (3H, s), 2.13 (1H, t, J = 5.5 Hz).

10 (4-Bromo-2-methyl-benzyloxy)-trimethylsilane (**Intermediate 134**)

11 To a solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**
12 **133**, 500.0 mg, 2.48 mmols), in 10 mL THF was added triethylamine (374.0
13 mg, 3.70 mmols) and chlorotrimethylsilane (297.0 mg, 2.70 mmols). The
14 resulting solution was stirred for 17 hours at 25 °C and then treated with
15 H₂O and extracted with Et₂O. The combined organic layers were washed
16 with H₂O, 10% aqueous HCl, saturated NaHCO₃, and saturated NaCl before
17 being dried (MgSO₄) and concentrated under reduced pressure. The title
18 compound, 550.0 mg (81%), was isolated by column chromatography (5%
19 EtOAc-hexanes) as a colorless oil.

20 ¹H NMR (CDCl₃) δ: 7.35-7.28 (3H, m), 4.64 (2H, s), 2.29 (3H, s), 0.20 (9H,
21 s).

22 2-Methyl-4-trimethylsilanylethynyl-1-trimethylsilanyloxymethyl-benzene
23 (**Intermediate 135**)

24 Using General Procedure D; (4-bromo-2-methyl-benzyloxy)-
25 trimethylsilane (**Intermediate 134**, 550.0 mg, 2.01 mmol) in triethylamine
26 (8 mL) was treated with copper(I)iodide (38.0 mg, 0.20 mmol) and then
27 sparged with argon for 5 minutes. Trimethylsilyl acetylene (1.05 g, 10.6

1 mmols) was then added followed by
2 dichlorobis(triphenylphosphine)palladium(II) (142.0 mg, 0.20 mmol). The
3 resulting reaction mixture was heated to 70 °C for 5 days. The title
4 compound (380.0 mg, 65%) was isolated by chromatography (0 - 2% EtOAc
5 - hexanes) as an orange oil.

6 ¹H NMR (CDCl₃) δ: 7.31 (3H, m), 4.64 (2H, s), 2.24 (3H, s), 0.24 (9H, s),
7 0.15 (9H, s).

8 (4-Ethynyl-2-methyl-phenyl)-methanol (**Intermediate 136**)

9 Using General Procedure E; 2-methyl-4-trimethylsilanylethynyl-1-
10 trimethylsilanyloxymethyl-benzene (**Intermediate 135**, 380.0 mg, 1.30
11 mmols) in methanol (10 mL) was treated with potassium carbonate (180.0
12 mg, 1.3 mmol) and stirred overnight at ambient temperature. The crude
13 alkyne was purified by column chromatography (5-20% EtOAc-hexanes) to
14 give 100.0 mg (34%) of the title compound.

15 ¹H NMR (CDCl₃) δ: 7.06 (3H, m), 4.42 (2H, d, J = 5.2 Hz), 2.81 (1H, s),
16 2.05 (3H, s), 1.59 (1H, t, J = 5.2 Hz).

17 Ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-benzoate (**Compound**
18 **117, General Formula 6**)

19 Using General Procedure F; (4-ethynyl-2-methyl-phenyl)-methanol
20 (**Intermediate 136**, 100.0 mg, 0.44 mmol) and ethyl-4-iodo benzoate
21 (**Reagent A**, 125.0 mg, 0.45 mmol) in triethyl amine (4 mL) was treated
22 with copper(I)iodide (29 mg, 0.15 mmol) and sparged with argon for 5
23 minutes. Dichlorobis(triphenylphosphine)palladium(II) (102 mg, 0.15
24 mmol) was added and the reaction mixture was stirred overnight at room
25 temperature. Column chromatography (20-40% EtOAc - hexanes) afforded
26 130.0 mg (99%) of the title compound as an orange solid.

27 ¹H NMR (CDCl₃) δ: 7.98 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.36

1 (3H, m), 4.65 (2H, s), 4.36 (2H, q, J = 7.1 Hz), 2.40 (1H, s), 2.30 (3H, s),
2 1.39 (3H, t, J = 7.1 Hz).

3 Ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate (**Intermediate**
4 **137**)

5 A solution of ethyl 4-(4-hydroxymethyl-3-methyl-phenylethynyl)-
6 benzoate (**Compound 117**, 130.0 mg, 0.44 mmol) and triphenylphosphine
7 (150.0 mg, 0.57 mmol) in 5 mL CH₂Cl₂ was cooled to 0 °C and *N*-
8 bromosuccinimide (101.0 mg, 0.57 mmol) was added in 5 portions over 20
9 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The
10 reaction was quenched by the addition of dilute aqueous NaHCO₃. The
11 resulting mixture was extracted with Et₂O and the combined organic layers
12 were washed with H₂O and saturated aqueous NaCl before being dried
13 (Na₂SO₄) and concentrated under reduced pressure. The title compound,
14 120.0 mg (76%), was isolated by column chromatography (2-5% EtOAc-
15 hexanes) as a colorless solid.
16 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.1 Hz), 7.32
17 (3H, m), 4.48 (2H, s), 4.38 (2H, q, J = 7.1 Hz), 2.40 (3H, s), 1.39 (3H, t, J =
18 7.1 Hz).

19 Ethyl 4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoate
20 (**Compound 118, General Formula 6**)

21 A solution of imidazole (30.0 mg, 0.44 mmol) in 2 mL DMF was
22 treated with NaH (11.0 mg, 0.44 mmol) and heated to 90 °C. After 1h a
23 solution of ethyl 4-(4-bromomethyl-3-methyl-phenylethynyl)-benzoate
24 (**Intermediate 137**, 120.0 mg, 0.34 mmol) in 2 mL DMF was added and
25 stirring at 90 °C continued for 1 hour. The solution was cooled to room
26 temperature and concentrated under reduced pressure. The title compound,
27 90.0 mg (71%) was isolated by column chromatography (20-100% EtOAc-

1 hexanes) as a colorless solid.

2 ¹H NMR (CDCl₃) δ: 8.02 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.51
3 (1H, s), 7.40 (1H, s), 7.36 (1H, dd, J = 1.2, 7.9 Hz), 7.10 (1H, s), 6.93 (1H,
4 d, J = 7.9 Hz), 6.88 (1H, t, J = 1.7 Hz), 5.12 (2H, s), 4.38 (2H, q, J = 7.1
5 Hz), 2.27 (3H, s), 1.40 (3H, t, J = 7.1 Hz).

6 4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-benzoic acid
7 **(Compound 119, General Formula 6)**

8 Using General Procedure I; a solution of ethyl 4-(4-imidazol-1-
9 ylmethyl-3-methyl-phenylethynyl)-benzoate (**Compound 118**, 82.0 mg,
10 0.24 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was treated with
11 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred
12 overnight at room temperature. Work-up afforded 51.0 mg (68%) of the
13 title compound as a solid.

14 ¹H NMR (d₆-DMSO) δ: 9.20 (1H, s), 7.97 (2H, d, J = 8.2 Hz), 7.73 (2H, m),
15 7.65 (2H, d, J = 8.2 Hz), 7.52 (1H, s), 7.46 (1H, d, J = 7.9 Hz), 7.13 (1H, d,
16 J = 7.9 Hz), 5.50 (2H, s), 2.32 (3H, s).

17 4-Bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**)

18 A solution of (4-bromo-2-methyl-phenyl)-methanol (**Intermediate**
19 **133**, 319.0 mg, 1.58 mmol) and triphenylphosphine (466.0 mg, 1.74 mmol)
20 in 5 mL CH₂Cl₂ was cooled to 0 °C and *N*-bromosuccinimide (309.0 mg,
21 1.74 mmol) was added in 5 portions over 20 minutes. The solution was
22 warmed to 25 °C and stirred for 17 hours. The reaction was quenched by
23 the addition of dilute aqueous NaHCO₃. The resulting mixture was
24 extracted with Et₂O and the combined organic layers were washed with H₂O
25 and saturated aqueous NaCl before being dried (Na₂SO₄) and concentrated
26 under reduced pressure. The title compound, 350.0 mg (84%), was isolated
27 by column chromatography (2-3% EtOAc-hexanes) as a colorless oil.

¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 2.0 Hz), 7.29 (1H, dd, J = 2.0, 7.9 Hz), 7.15 (1H, d, J = 7.9 Hz), 4.43 (2H, s), 2.37 (3H, s).

1-(4-Bromo-2-methyl-benzyl)-1H-imidazole (Intermediate 139)

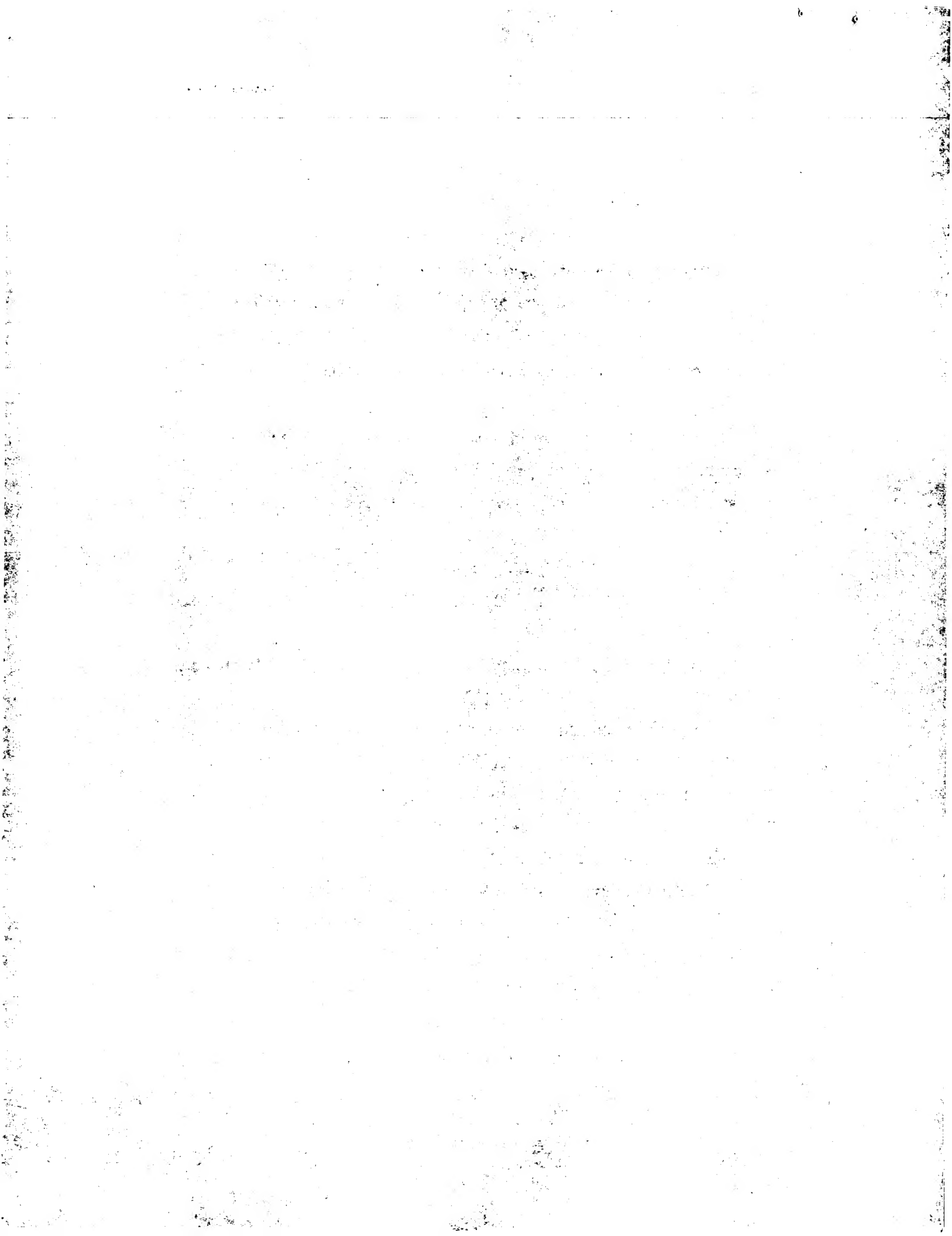
A solution of imidazole (58.0 mg, 0.86 mmol) in 3 mL DMF was treated with NaH (20.0 mg, 0.86 mmol) and heated to 90 °C. After 1h a solution of 4-bromo-1-bromomethyl-2-methyl-benzene (**Intermediate 138**, 190.0 mg, 0.72 mmol) in 3 mL DMF was added and stirring at 90 °C continued for 1hour. The solution was cooled to room temperature and concentrated under reduced pressure. The title compound, 160.0 mg (88%) was isolated by column chromatography (5% MeOH-EtOAc) as a colorless solid.

¹H NMR (CDCl₃) δ: 7.46 (1H, s), 7.34 (1H, dd, J = 1.8 Hz), 7.30 (1H, dd, J = 1.8, 8.2 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.83 (1H, t, J = 1.2 Hz), 6.80 (1H, d, J = 8.2 Hz), 5.03 (2H, s), 2.23 (3H, s).

1-(2-Methyl-4-trimethylsilanylethynyl-benzyl)-1H-imidazole (Intermediate 140)

Using General Procedure D; 1-(4-bromo-2-methyl-benzyl)-1H-imidazole (**Intermediate 139**, 160.0 mg, 0.64 mmol) in triethylamine (8 mL) was treated with copper(I)iodide (12.0 mg, 0.07 mmol) and then sparged with argon for 5 minutes. Trimethylsilyl acetylene (0.70 g, 0.71 mmols) was then added followed by dichlorobis(triphenylphosphine)palladium(II) (45.0 mg, 0.07 mmol). The resulting reaction mixture was heated to 70 °C for 5 days. The title compound (140.0 mg, 82%) was isolated by chromatography (5% MeOH-EtOAc) as an orange oil.

¹H NMR (CDCl₃) δ: 7.53 (1H, s), 7.38 (1H, s), 7.34 (1H, d, J = 8.0 Hz), 7.15 (1H, s), 6.94 (1H, s), 6.91 (1H, d, J = 8.0 Hz), 5.14 (2H, s), 2.29 (3H,



1 s), 0.31 (9H, s).

2 1-(4-Ethynyl-2-methyl-benzyl)-1H-imidazole (Intermediate 141)

3 Using General Procedure E; 1-(2-methyl-4-trimethylsilanylethynyl-
4 benzyl)-1H-imidazole (**Intermediate 140**, 140.0 mg, 0.53 mmols) in
5 methanol (5 mL) was treated with potassium carbonate (100.0 mg, 0.72
6 mmol) and stirred overnight at ambient temperature. The crude alkyne (105
7 mg, 100%) was used directly in the next reaction.

8 ¹H NMR (CDCl₃) δ: 7.49 (1H, s), 7.35 (1H, s), 7.31 (1H, dd, J = 1.7, 7.9
9 Hz), 7.10 (1H, s), 6.69 (1H, d, J = 7.9 Hz), 6.85 (1H, t, J = 1.2 Hz), 5.14
10 (2H, s), 3.08 (1H, s), 2.26 (3H, s).

11 Methyl [4-(4-imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetate
12 (**Compound 120, General Formula 6**)

13 Using General Procedure F; 1-(4-ethynyl-2-methyl-benzyl)-1H-
14 imidazole (**Intermediate 141**, 101.0 mg, 0.53 mmol) and methyl-(4-
15 iodophenyl)-acetate (**Reagent B**, 145.0 mg, 0.53 mmol) in triethylamine (5
16 mL) was treated with copper(I)iodide (34.0 mg, 0.18 mmol) and sparged
17 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
18 (124 mg, 0.18 mmol) was added and the reaction mixture was stirred
19 overnight at room temperature. Column chromatography (5% MeOH-
20 EtOAc) afforded 45.0 mg (25%) of the title compound as an orange oil.

21 ¹H NMR (CDCl₃) δ: 7.47 (3H, m), 7.35 (3H, m), 7.27 (3H, m), 6.91 (1H, d,
22 J = 7.3 Hz), 5.11 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 2.26 (3H, s).

23 [4-(4-Imidazol-1-yl-methyl-3-methyl-phenylethynyl)-phenyl]-acetic acid
24 (**Compound 121, General Formula 6**)

25 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-
26 ylmethyl-3-methyl-phenylethynyl)-phenyl]-acetate (**Compound 120**, 45.0
27 mg, 0.13 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was treated

1 with NaOH (80.0 mg, 2.0 mmols, 2.0 mL of a 1N aqueous solution) and
2 stirred overnight at room temperature. Work-up afforded 30.0 mg (70%) of
3 the title compound as a pale-orange solid.

4 ¹H NMR (d₄-MeOH) δ: 8.97 (1H, s), 7.60 (2H, d J = 8.8 Hz), 7.47 (3H, m),
5 7.41 (1H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.23 (1H, d, J = 7.9 Hz),
6 5.51 (2H, s), 3.64 (2H, s), 2.33 (3H, s).

7 1-Isopropyl-3-methoxy-benzene (Intermediate 142)

8 To a solution of 3-isopropyl-phenol (5.00 g, 36.2 mmols) in 50 mL of
9 acetone was added K₂CO₃ (7.50 g, 54.3 mmols) and iodomethane (10.3 g,
10 72.5 mmols). The resulting solution was heated to 50 °C and stirred for 18
11 hours, cooled to room temperature, and concentrated under reduced
12 pressure. The residual oil was dissolved in Et₂O and washed with H₂O,
13 saturated aqueous NaHCO₃, and saturated aqueous NaCl before being dried
14 (MgSO₄) and concentrated under reduced pressure. The crude methyl ether
15 was used without further purification.

16 ¹H NMR (CDCl₃) δ: 7.22 (1H, t, J = 8.1 Hz), 6.84-6.72 (3H, m), 3.81 (3H,
17 s), 2.88 (1H, septet, J = 7.0 Hz), 1.25 (6H, d, J = 7.0 Hz).

18 1-Bromo-2-isopropyl-4-methoxy-benzene (Intermediate 143)

19 A mixture of 1-isopropyl-3-methoxy-benzene (**Intermediate 142**,
20 3.50 g, 23.3 mmols), molecular sieves, and silica gel in 150 mL CCl₄ was
21 treated with *N*-bromosuccinimide (4.98 g, 28.0 mmols) at 35 °C for 18
22 hours. An additional portion of *N*-bromosuccinimide (830.0 mg, 4.46
23 mmols) was added and stirring continued for 6 hours. The mixture was
24 cooled to room temperature, H₂O was added, and the mixture was filtered to
25 remove the solids. The mixture was extracted with E₂O and the combined
26 organic layers were washed with 10% aqueous HCl, H₂O, saturated aqueous
27 NaHCO₃, and saturated NaCl before being dried (MgSO₄) and concentrated

1 under reduced pressure. Column chromatography (2.5% EtOAc-hexanes)
2 afforded 4.34 g (81%) of the title compound as a pale-yellow oil.
3 ¹H NMR (CDCl₃) δ: 7.41 (1H, d, J = 8.8 Hz), 6.82 (1H, d, J = 2.6 Hz), 6.61
4 (1H, dd, J = 2.6, 8.8 Hz), 3.79 (3H, s), 3.31 (1H, septet, J = 6.7 Hz), 1.23
5 (6H, d, J = 6.7 Hz).

6 4-Bromo-3-isopropyl-phenol (**Intermediate 144**)

7 To a solution of 1-bromo-2-isopropyl-4-methoxy-benzene
8 (**Intermediate 143**, 2.20 g, 9.60 mmols) in 50 mL CH₂Cl₂ at -78 °C was
9 added BBr₃ (4.81 g, 19.2 mmols; 19.2 mL of a 1M solution in CH₂Cl₂).
10 After stirring for 3 hours at -78 °C the solution was warmed to 0 °C for 3
11 hours and then at 25 °C for 1 hour before being quenched with H₂O. The
12 mixture was diluted with Et₂O and washed with H₂O and saturated aqueous
13 NaCl, dried (Na₂SO₄) and concentrated under reduced pressure. Column
14 chromatography (2.5-10% EtOAc-hexanes) afforded the title compound as a
15 colorless oil.
16 ¹H NMR (CDCl₃) δ: 7.38 (1H, d, J = 8.5 Hz), 6.79 (1H, d, J = 2.9 Hz), 6.57
17 (1H, dd, J = 2.9, 8.5 Hz), 3.31 (1H, septet, J = 7.0 Hz), 1.22 (6H, d, J = 7.0
18 Hz).

19 (4-Bromo-3-isopropyl-phenoxy)-tert-butyl-dimethyl-silane (**Intermediate**
20 **145**)

21 A solution of 4-bromo-3-isopropyl-phenol (**Intermediate 144**, 1.13
22 g, 5.25 mmols), chloro-*tert*-butyl-dimethylsilane (0.95 g, 6.30 mmols), and
23 imidazole (428.0 mg, 6.3 mmols) in 10 mL DMF was stirred at 25 °C for 3
24 hours. The solution was diluted with H₂O and extracted with Et₂O and the
25 combined organic layers were washed with H₂O, saturated aqueous NaCl,
26 and dried (MgSO₄) before being concentrated under reduced pressure.
27 Column chromatography (1-2% EtOAc-hexanes) afforded 1.50 g (87%) of

1 the title compound as a colorless oil.

2 ¹H NMR (CDCl₃) δ: 7.32 (1H, d, J = 8.8 Hz), 6.73 (1H, d, J = 3.0 Hz), 6.52
3 (1H, dd, J = 3.0, 8.8 Hz), 3.26 (1H, septet, J = 6.7 Hz), 1.19 (6H, d, J = 6.7
4 Hz), 0.96 (9H, s), 0.17 (6H, s).

5 4-(*Tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-benzaldehyde
6 (**Intermediate 146**)

7 A solution of (4-bromo-3-isopropyl-phenoxy)-*tert*-butyl-dimethyl-
8 silane (**Intermediate 145**, 1.03 g, 3.13 mmols) in 25 mL E₂O was cooled to
9 -78 °C and treated with *tert*-butyllithium (401.0 mg, 6.26 mmols; 3.7 mL of
10 a 1.7M solution in pentane). After 30 minutes the reaction was quenched
11 with DMF (913.0 mg, 12.5 mmols) and warmed to room temperature. The
12 solution was diluted with H₂O, extracted with Et₂O and the combined
13 organic layers washed with H₂O and saturated aqueous NaCl before being
14 dried (MgSO₄) and concentrated under reduced pressure. Column
15 chromatography (2% EtOAc-hexanes) afforded 480.0 mg (55%) of the title
16 compound as a colorless oil.

17 ¹H NMR (CDCl₃) δ: 10.19 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J =
18 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.5 Hz), 3.97 (1H, septet, J = 6.7 Hz), 1.27
19 (6H, d, J = 6.7 Hz), 1.00 (9H, s), 0.25 (6H, s).

20 4-Hydroxy-2-isopropyl-benzaldehyde (**Intermediate 147**)

21 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-isopropyl-
22 benzaldehyde (**Intermediate 146**, 880.0 mg, 3.17 mmols) in 6 mL THF at 0
23 °C was added tetrabutylammonium fluoride (1.66 g, 6.33 mmols; 6.3 mL of
24 a 1M solution in THF). The pale-yellow solution was stirred for 30 minutes
25 and quenched by the addition of ice cold H₂O. The mixture was extracted
26 with Et₂O and the combined organic layers were washed with H₂O and
27 saturated aqueous NaCl before being dried (Na₂SO₄) and concentrated under

1 reduced pressure. Column chromatography (20% EtOAc-hexanes) afforded
2 500.0 mg (96%) of the title compound as a colorless solid.
3 ¹H NMR (CDCl₃) δ: 10.15 (1H, s), 7.79 (1H, d, J = 8.5 Hz), 6.95 (1H, d, J =
4 2.3 Hz), 6.86 (1H, dd, J = 2.3, 8.5 Hz), 3.96 (1H, septet, J = 6.7 Hz), 1.29
5 (6H, d, J = 6.7 Hz).

6 4-Formyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate
7 **(Intermediate 148)**

8 A solution of 4-hydroxy-2-isopropyl-benzaldehyde (**Intermediate**
9 **147**, 300.0 mg, 1.83 mmol) in 10 mL of CH₂Cl₂ was cooled to 0 °C and to it
10 was added 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine
11 (754.0 mg, 1.92 mmol) and triethylamine (592.0 mg, 5.85 mmols). The
12 resulting solution was warmed to room temperature and stirred for 4.5
13 hours. The reaction was quenched by the addition of H₂O and the mixture
14 extracted with EtOAc and the combined organic layers were washed with
15 10% aqueous HCl, saturated aqueous NaHCO₃, H₂O, and saturated aqueous
16 NaCl. The solution was dried (MgSO₄) and concentrated under reduced
17 pressure. The title compound was isolated by column chromatography (5-
18 10% EtOAc-hexanes) as a colorless oil, 470.0 mg (87%).
19 ¹H NMR (CDCl₃) δ: 10.37 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.33 (1H, d, J =
20 2.3 Hz), 7.26 (1H, dd, J = 2.3, 8.5 Hz), 4.00 (1H, septet, J = 6.7 Hz), 1.33
21 (6H, d, J = 6.7 Hz),

22 4-Hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-methansulfonate
23 **(Intermediate 149)**

24 To a solution of 4-formyl-3-isopropyl-phenyl 1,1,1-trifluoro-
25 methansulfonate (**Intermediate 148**, 540.0 mg, 1.82 mmols) in 7 mL
26 MeOH at 0 °C was added NaBH₄ (72.0 mg, 1.91 mmols). After stirring 2
27 hours at 0 °C the reaction was carefully quenched with H₂O and extracted

1 with Et₂O. The combined organic layers were washed with H₂O and
2 saturated aqueous NaCl, dried (MgSO₄), and concentrated under reduced
3 pressure. The title compound was isolated by column chromatography (5-
4 10% EtOAc-hexanes) as a colorless oil, 355.0 mg (90%).
5 ¹H NMR (CDCl₃) δ: 7.45 (1H, d, J = 8.5 Hz), 7.17 (1H, d, J = 2.7 Hz), 7.08
6 (1H, dd, J = 2.7, 8.5 Hz), 4.74 (2H, d, J = 5.3 Hz), 3.21 (1H, septet, J = 7.0
7 Hz), 2.12 (1H, t, J = 5.3 Hz), 1.24 (6H, d, J = 7.0 Hz).

8 4-(*Tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-phenyl 1,1,1-
9 trifluoro-methansulfonate (**Intermediate 150**)

10 A solution of 4-hydroxymethyl-3-isopropyl-phenyl 1,1,1-trifluoro-
11 methansulfonate (**Intermediate 149**, 760.0 mg, 2.55 mmols), chloro-*tert*-
12 butyl-dimethylsilane (470.0 mg, 3.18 mmols), and imidazole (225.0 mg,
13 3.25 mmols) in 6 mL DMF was stirred at 25 °C for 17 hours. The solution
14 was diluted with H₂O and extracted with Et₂O and the combined organic
15 layers were washed with 10% aqueous HCl, saturated aqueous NaHCO₃,
16 H₂O, and saturated aqueous NaCl, and dried (MgSO₄) before being
17 concentrated under reduced pressure. Column chromatography (2-5%
18 EtOAc-hexanes) afforded 970.0 mg (92%) of the title compound as a
19 colorless oil.

20 ¹H NMR (CDCl₃) δ: 7.49 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 2.3 Hz), 7.06
21 (1H, dd, J = 2.3, 8.5 Hz), 4.75 (2H, s), 3.10 (1H, septet, J = 6.7 Hz), 1.21
22 (6H, d, J = 6.7 Hz), 0.93 (9H, s), 0.10 (6H, s).

23 1-(*Tert*-butyl-dimethyl-silanyloxymethyl)-2-isopropyl-4-
24 trimethylsilanylethynyl-benzene (**Intermediate 151**)

25 To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-
26 isopropyl-phenyl 1,1,1-trifluoro-methansulfonate (**Intermediate 150**, 970.0
27 mg, 2.35 mmols) in triethylamine (2 mL) and 6 mL DMF was sparged with

1 argon for 15 minutes. Trimethylsilyl acetylene (1.00 g, 10.6 mmols) was
2 then added followed by dichlorobis(triphenylphosphine)palladium(II) (66.0
3 mg, 0.09 mmol). The resulting reaction mixture was heated to 95 °C for 20
4 hours. The solution was cooled to room temperature and concentrated under
5 reduced pressure. The title compound (200.0 mg, 78%) was isolated by
6 chromatography (0-25% EtOAc-hexanes) as an orange oil.
7 ¹H NMR (CDCl₃) δ: 7.37-7.25 (3H, m), 4.75 (2H, s), 3.08 (1H, septet, J =
8 7.0 Hz), 1.21 (6H, d, J = 7.0 Hz), 0.92 (9H, s), 0.25 (9H, s), 0.09 (6H, s).

9 *Tert*-butyl-(4-ethynyl-2-isopropyl-benzyloxy)-dimethyl-silane
10 **(Intermediate 152)**

11 Using General Procedure E; 1-(*tert*-butyl-dimethyl-
12 silanyloxymethyl)-2-isopropyl-4-trimethylsilanylethynyl-benzene
13 **(Intermediate 151**, 850.0 mg, 2.36 mmols) in methanol (25 mL) was
14 treated with potassium carbonate (250.0 mg, 1.81 mmols) and stirred
15 overnight at ambient temperature. The crude alkyne (650 mg, 95%) was
16 used directly in the next reaction.

17 ¹H NMR (CDCl₃) δ: 7.41-7.25 (3H, m), 4.77 (2H, s), 3.07 (1H, septet, J =
18 7.0 Hz), 3.05 (1H, s), 1.22 (6H, d, J = 7.0 Hz), 0.94 (9H, s), 0.11 (6H, s).

19 Ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-
20 phenylethynyl]-benzoate **(Intermediate 153)**

21 Using General procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-
22 benzyloxy)-dimethyl-silane **(Intermediate 152**, 300.0 mg, 1.04 mmols) and
23 ethyl-4-iodo benzoate **(Reagent A**, 287.0 mg, 1.04 mmols) in triethylamine
24 (8mL) was treated with copper(I)iodide (50.0 mg, 0.26 mmol) and sparged
25 with argon for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II)
26 (182 mg, 0.26 mmol) was added and the reaction mixture was stirred
27 overnight at room temperature. Column chromatography (2-4% EtOAc -

1 hexanes) afforded 310.0 mg (68%) of the title compound as an orange solid.

2 .

3 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.48-
4 7.37 (3H, m), 4.80 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.14 (1H, septet, J = 6.8
5 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.27 (6H, d, J = 6.8 Hz), 0.96 (9H, s), 0.12
6 (6H, s).

7 Methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-
8 phenylethynyl]-phenyl}-acetate (Intermediate 154)

9 Using General Procedure F; *tert*-butyl-(4-ethynyl-2-isopropyl-
10 benzyloxy)-dimethyl-silane (Intermediate 152, 355.0 mg, 1.26 mmols) and
11 methyl-(4-iodophenyl)-acetate (Reagent B, 349.0 mg, 1.26 mmols) in
12 triethylamine (8 mL) was treated with copper(I)iodide (60.0 mg, 0.32 mmol)
13 and sparged with argon for 5 minutes.

14 Dichlorobis(triphenylphosphine)palladium(II) (222 mg, 0.32 mmol) was
15 added and the reaction mixture was stirred overnight at room temperature.
16 Column chromatography (2-5% EtOAc-hexanes) afforded 288.0 mg (66%)
17 of the title compound as an orange oil.

18 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.5 Hz), 7.43-7.35 (3H, m), 7.25 (2H,
19 d, J = 8.5 Hz), 4.77 (2H, s), 3.69 (3H, s), 3.63 (2H, s), 3.11 (1H, septet, J =
20 6.7 Hz), 1.25 (6H, d, J = 6.7 Hz), 0.94 (9H, s), 0.10 (6H, s).

21 Ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-benzoate
22 (Compound 122, General Formula 6)

23 To a solution of ethyl 4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-
24 isopropyl-phenylethynyl]-benzoate (Intermediate 153, 310.0 mg, 0.71
25 mmol) in 4 mL THF at 0 °C was added tetrabutylammonium fluoride (371.0
26 mg, 1.42 mmols; 1.4 mL of a 1M solution in THF). The pale-yellow
27 solution was stirred for 10 minutes and quenched by the addition of ice cold

1 H₂O. The mixture was extracted with Et₂O and the combined organic layers
2 were washed with H₂O and saturated aqueous NaCl before being dried
3 (Na₂SO₄) and concentrated under reduced pressure. Column
4 chromatography (20-30% EtOAc-hexanes) afforded 200.0 mg (87%) of the
5 title compound as a colorless solid.

6 ¹H NMR (CDCl₃) δ: 7.98 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.48
7 (1H, s), 7.35 (2H, m), 4.71 (2H, s), 4.35 (2H, q, J = 7.1 Hz), 3.19 (1H,
8 septet, J = 7.0 Hz), 2.51 (1H, s), 1.39 (3H, t, J = 7.1 Hz), 1.25 (6H, d, J = 7.0
9 Hz).

10 Methyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate
11 **(Compound 123, General Formula 6)**

12 To a solution of methyl {4-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-
13 3-isopropyl-phenylethynyl]-phenyl}-acetate (**Intermediate 154**, 288.0 mg,
14 0.66 mmol) in 5 mL THF at 0 °C was added tetrabutylammonium fluoride
15 (471.0 mg, 1.80 mmols; 1.8 mL of a 1M solution in THF). The pale-yellow
16 solution was stirred for 15 minutes and quenched by the addition of ice cold
17 H₂O. The mixture was extracted with Et₂O and the combined organic layers
18 were washed with H₂O and saturated aqueous NaCl before being dried
19 (Na₂SO₄) and concentrated under reduced pressure. Column
20 chromatography (5-10% EtOAc-hexanes) afforded 180.0 mg (85%) of the
21 title compound as a colorless solid.

22 ¹H NMR (CDCl₃) δ: 7.48 (3H, m), 7.32 (2H, m), 7.24 (2H, d, J = 8.5 Hz),
23 4.69 (2H, s), 3.68 (3H, s), 3.62 (2H, s), 3.18 (1H, septet, J = 7.0 Hz), 2.21
24 (1H, s), 1.25 (6H, d, J = 7.0 Hz).

25 Ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-benzoate
26 **(Intermediate 155)**

27 A solution of ethyl [4-(4-hydroxymethyl-3-isopropyl-phenylethynyl)-

1 benzoate (**Compound 122**, 200.0 mg, 0.62 mmol) and triphenylphosphine
2 (211.0 mg, 0.81 mmol) in 5 mL CH₂Cl₂ was cooled to 0 °C and *N*-
3 bromosuccinimide (144.0 mg, 0.81 mmol) was added in 5 portions over 20
4 minutes. The solution was warmed to 25 °C and stirred for 17 hours. The
5 reaction was quenched by the addition of dilute aqueous NaHCO₃. The
6 resulting mixture was extracted with Et₂O and the combined organic layers
7 were washed with H₂O and saturated aqueous NaCl before being dried
8 (Na₂SO₄) and concentrated under reduced pressure. The title compound,
9 220.0 mg (93%), was isolated by column chromatography (5% EtOAc-
10 hexanes) as a pale-yellow solid.

11 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.48
12 (1H, s), 7.31 (2H, m), 4.55 (2H, s), 4.39 (2H, q, J = 7.1 Hz), 3.29 (1H, septet,
13 J = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.30 (6H, d, J = 7.0 Hz).

14 Methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate
15 (**Intermediate 156**)

16 A solution of methyl [4-(4-hydroxymethyl-3-isopropyl-
17 phenylethynyl)-phenyl]-acetate (**Compound 123**, 180.0 mg, 0.56 mmol) and
18 triphenylphosphine (190.0 mg, 0.73 mmol) in 5 mL CH₂Cl₂ was cooled to 0
19 °C and *N*-bromosuccinimide (130.0 mg, 0.73 mmol) was added in 5 portions
20 over 20 minutes. The solution was warmed to 25 °C and stirred for 17
21 hours. The reaction was quenched by the addition of dilute aqueous
22 NaHCO₃. The resulting mixture was extracted with Et₂O and the combined
23 organic layers were washed with H₂O and saturated aqueous NaCl before
24 being dried (Na₂SO₄) and concentrated under reduced pressure. The title
25 compound, 212.0 mg (98%), was isolated by column chromatography (5-
26 10% EtOAc-hexanes) as a pale-yellow oil.

27 ¹H NMR (CDCl₃) δ: 7.48 (3H, m), 7.28 (4H, m), 4.55 (2H, s), 3.69 (3H, s),

1 3.63 (2H, s), 3.28 (1H, septet, J = 7.0 Hz), 1.30 (6H, d, J = 7.0 Hz).

2 Ethyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-
3 benzoate (**Compound 124, General Formula 6**)

4 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
5 benzoate (**Intermediate 155**, 120.0 mg, 0.31 mmol) and 1-acetylimidazole
6 (36.0 mg, 0.33 mmol) in 5 mL CH₃CN was heated at 65 °C for 4 hours and
7 then at 55 °C for 16 hours. The solution was cooled to room temperature,
8 diluted with H₂O and made basic by addition of Na₂CO₃, and extracted with
9 EtOAc. The combined organic layers were washed with H₂O and saturated
10 aqueous NaCl, dried (MgSO₄), and concentrated under reduced pressure.
11 Column chromatography (1% Et₃N in 5% MeOH-EtOAc) afforded 75.0 mg
12 (65%) of the title compound as a colorless solid.

13 ¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.53
14 (1H, d, J = 1.5 Hz), 7.49 (1H, s), 7.35 (1H, dd, J = 1.5, 7.9 Hz), 7.09 (1H,
15 bs), 6.98 (1H, d, J = 7.9 Hz), 6.85 (1H, bs), 5.19 (2H, s), 4.39 (2H, q, J = 7.1
16 Hz), 3.08 (1H, septet, J = 6.8 Hz), 1.40 (3H, t, J = 7.1 Hz), 1.20 (6H, d, J =
17 6.8 Hz).

18 Methyl [4-(4-imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-
19 acetate (**Compound 125, General Formula 6**)

20 A solution of methyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
21 phenyl]-acetate (**Intermediate 156**, 72.0 mg, 0.19 mmol) and 1-
22 acetylimidazole (22.0 mg, 0.20 mmol) in 5 mL CH₃CN was heated at 65 °C
23 for 8h and then at 55 °C for 16 hours. The solution was cooled to room
24 temperature, diluted with H₂O and made basic by addition of Na₂CO₃, and
25 extracted with EtOAc. The combined organic layers were washed with H₂O
26 and saturated aqueous NaCl, dried (MgSO₄), and concentrated under
27 reduced pressure. Column chromatography (0.5% Et₃N in 5% MeOH-

1 EtOAc) afforded 40.0 mg (58%) of the title compound as a colorless solid.
2 ¹H NMR (CDCl₃) δ: 7.49 (4H, m), 7.33 (1H, dd, J = 1.5, 7.9 Hz), 7.28 (2H,
3 d, J = 8.5 Hz), 7.08 (1H, t, J = 1.2 Hz), 6.95 (1H, d, J = 7.9 Hz), 6.84 (1H, t,
4 J = 1.2 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.64 (2H, s), 3.06 (1H, septet, J = 6.8
5 Hz), 1.20 (6H, d, J = 6.8 Hz).

6 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-benzoic
7 acid (Compound 126, General Formula 6)

8 Using General Procedure I; a solution of ethyl [4-(4-imidazol-1-
9 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-benzoate (Compound 124,
10 75.0 mg, 0.20 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was
11 treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution)
12 and stirred overnight at room temperature. Work-up afforded 68.0 mg
13 (88%) of the title compound as a colorless solid.

14 ¹H NMR (d₄-MeOH) δ: 9.01 (1H, s), 8.01 (2H, d, J = 8.2 Hz), 7.63-7.57
15 (5H, m), 7.44 (1H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 5.59 (2H, s),
16 3.17 (1H, septet, J = 6.8 Hz), 1.20 (6H, d, J = 6.8 Hz).

17 [4-(4-Imidazol-1-yl-methyl-3-isopropyl-phenylethynyl)-phenyl]-acetic acid
18 (Compound 127, General Formula 6)

19 Using General Procedure I; a solution of methyl [4-(4-imidazol-1-
20 ylmethyl-3-isopropyl-phenylethynyl)-phenyl]-acetate (Compound 125, 40.0
21 mg, 0.11 mmol) in ethanol (4 mL) and tetrahydrofuran (1 mL) was treated
22 with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and
23 stirred overnight at room temperature. Work-up afforded 22.0 mg (52%) of
24 the title compound as a colorless solid.

25 ¹H NMR (d₄-MeOH) δ: 9.02 (1H, bs), 7.62 (1H, t, J = 1.4 Hz), 7.58 (2H, m),
26 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.31 (3H, m), 5.58
27 (2H, s), 3.68 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.18 (6H, d, J = 6.7 Hz).

1 4-Bromo-*N*-cyclopropyl-2-methyl-benzamide (**Intermediate 157**)

2 A solution of 4-bromo-2-methylbenzoic acid and SOCl_2 was refluxed
3 for 3 hours, cooled to room temperature and concentrated under reduced
4 pressure. The residue was dissolved in 30 mL CH_2Cl_2 and combined with
5 cyclopropyl amine (810.0 mg, 14.3 mmols) and pyridine (2.05 g, 26.0
6 mmols). The solution was stirred for 18 hours and then diluted with EtOAc
7 before being washed with 5% aqueous HCl, saturated NaHCO_3 , and
8 saturated aqueous NaCl. The solution was dried (MgSO_4) and concentrated
9 under reduced pressure leaving the title compound as a colorless solid.
10 ^1H NMR (CDCl_3) δ : 7.34 (1H, d, $J = 2.3$ Hz), 7.28 (1H, dd, $J = 2.3, 8.2$ Hz),
11 7.13 (1H, d, $J = 8.2$ Hz), 6.10 (1H, bs), 2.85 (1H, m), 2.37 (3H, s), 0.85 (2H,
12 m), 0.59 (2H, m).

13 (4-Bromo-2-methyl-benzyl)-cyclopropyl-amine (**Intermediate 158**)

14 To a solution of 4-bromo-*N*-cyclopropyl-2-methyl-benzamide
15 (**Intermediate 157**, 1.81 g, 7.12 mmols) in THF (12 mL) was added
16 $\text{BH}_3 \cdot \text{SMe}_2$ (1.08 g, 14.24 mmols). The solution was heated to 60 °C for 6
17 hours, cooled to room temperature and carefully treated with saturated
18 aqueous Na_2CO_3 (30 mL) and stirred for 17 hours. This mixture was
19 extracted with EtOAc and the combined organic layers were washed with
20 H_2O , saturated aqueous NaCl before being dried (MgSO_4) and concentrated
21 under reduced pressure. The title compound was isolated by column
22 chromatography (10-15% EtOAc-hexanes).
23 ^1H NMR (CDCl_3) δ : 7.26 (2H, m), 7.12 (1H, d, $J = 7.9$ Hz), 3.76 (2H, s),
24 2.31 (3H, s), 2.14 (1H, m), 0.44 (2H, m), 0.36 (2H, m).

25 (4-Bromo-2-methyl-benzyl)-cyclopropyl-ethyl-amine (**Intermediate 159**)

26 A mixture of (4-bromo-2-methyl-benzyl)-cyclopropyl-amine
27 (**Intermediate 158**, 600.0 mg, 2.49 mmols), ethyl iodide (1.56 g, 10.0

1 mmols), and K_2CO_3 (690.0 mg, 5.00 mmols) in 10 mL acetone was heated at
2 60 °C for 18 hours. The mixture was cooled to room temperature, diluted
3 with H_2O , and extracted with EtOAc. The combined organic layers were
4 washed with H_2O and saturated aqueous NaCl before being dried ($MgSO_4$)
5 and concentrated under reduced pressure. The title compound was isolated
6 by column chromatography (2.5% EtOAc-hexanes).
7 1H NMR ($CDCl_3$) δ : 7.23 (2H, m), 7.12 (1H, d, $J = 7.6$ Hz), 3.62 (2H, s),
8 2.56 (2H, q, $J = 7.3$ Hz), 2.29 (3H, s), 1.75 (1H, m), 1.04 (3H, t, $J = 7.3$ Hz),
9 0.39 (2H, m), 0.30 (2H, m).

10 Cyclopropyl-ethyl-(2-methyl-4-trimethylsilanylethynyl-benzyl)-amine
11 **(Intermediate 160)**

12 Using General Procedure D; (4-bromo-2-methyl-benzyl)-
13 cyclopropyl-ethyl-amine (**Intermediate 159**, 620.0 mg, 2.31 mmols) in
14 triethylamine (8 mL) was treated with copper(I)iodide (44.0 mg, 0.23 mmol)
15 and then sparged with argon for 15 minutes. Trimethylsilylacetylene (1.04
16 g, 10.6 mmols) was then added followed by dichlorobis-
17 (triphenylphosphine)palladium(II) (162.0 mg, 0.23 mmol). The resulting
18 reaction mixture was heated to 70 °C for 5 days. The title compound (650.0
19 mg, 98%) was isolated by chromatography (1-4% EtOAc - hexanes).
20 1H NMR ($CDCl_3$) δ : 7.32 (1H, s), 7.20 (2H, m), 3.65 (2H, s), 2.55 (2H, q, J
21 = 7.3 Hz), 2.28 (3H, s), 1.74 (1H, m), 1.03 (3H, t, $J = 7.3$ Hz), 0.36 (2H, m),
22 0.27 (2H, m), 0.24 (9H, s).

23 Cyclopropyl-ethyl-(4-ethynyl-2-methyl-benzyl)-amine (**Intermediate 161**)

24 Using General Procedure E; cyclopropyl-ethyl-(2-methyl-4-
25 trimethylsilanylethynyl-benzyl)-amine (**Intermediate 160**, 650.0 mg, 2.30
26 mmols) in methanol (10mL) was treated with potassium carbonate (100.0
27 mg, 0.72 mmol) and stirred overnight at ambient temperature. The crude

1 alkyne (495 mg, 99%) was used directly in the next reaction.
2 ¹H NMR (CDCl₃) δ: 7.32 (1H, s), 7.21 (2H, m), 3.66 (2H, s), 3.01 (1H, s),
3 2.56 (2H, q, J = 7.3 Hz), 2.29 (3H, s), 1.76 (1H, m), 1.04 (3H, t, J = 7.3 Hz),
4 0.40 (2H, m), 0.29 (2H, m).

5 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-
6 benzoate (**Compound 128, General Formula 6**)

7 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-
8 benzyl)-amine (**Intermediate 161**, 190.0 mg, 0.89 mmol) and ethyl-4-iodo
9 benzoate (**Reagent A**, 245.0 mg, 0.89 mmol) in triethylamine (5 mL) was
10 treated with copper(I)iodide (56.0 mg, 0.30 mmol) and sparged with argon
11 for 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (208 mg,
12 0.30 mmol) was added and the reaction mixture was stirred overnight at
13 room temperature. Column chromatography (3-5% EtOAc - hexanes)
14 afforded the title compound.

15 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.31-
16 7.24 (3H, m), 4.38 (2H, q, J = 7.1 Hz), 3.68 (2H, s), 2.58 (2H, q, J = 7.3
17 Hz), 2.32 (3H, s), 1.77 (1H, m), 1.39 (3H, t, J = 7.1 Hz), 1.05 (3H, t, J = 7.3
18 Hz), 0.39 (2H, m), 0.31 (2H, m).

19 Methyl (4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-
20 phenyl)-acetate) (**Compound 129, General Formula 6**)

21 Using General Procedure F; cyclopropyl-ethyl-(4-ethynyl-2-methyl-
22 benzyl)-amine (**Intermediate 161**, 300.0 mg, 1.41 mmols) and methyl-(4-
23 iodophenyl)-acetate (**Reagent B**, 388.0 mg, 1.41 mmols) in triethylamine (8
24 mL) was treated with copper(I)iodide (67.0 mg, 0.35 mmol) and sparged
25 with argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II)
26 (246 mg, 0.35 mmol) was added and the reaction mixture was stirred
27 overnight at room temperature. Column chromatography (5-7% EtOAc -

1 hexanes) afforded 270.0 mg (53%) of the title compound as a pale-yellow
2 oil.

3 ¹H NMR (CDCl₃) δ: 7.47 (2H, d, J = 7.9 Hz), 7.30-7.22 (5H, m), 3.70 (3H,
4 s), 3.68 (2H, s), 3.63 (2H, s), 2.58 (2H, q, J = 7.3 Hz), 2.32 (3H, s), 1.77
5 (1H, m), 1.05 (3H, t, J = 7.3 Hz), 0.39 (2H, m), 0.30 (2H, m).

6 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoic
7 acid: (**Compound 130, General Formula 6**)

8 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-
9 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-benzoate (**Compound 128**,
10 130.0 mg, 0.36 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL) was
11 treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous solution)
12 and stirred overnight at room temperature. Work-up afforded 115.0 mg
13 (96%) of the title compound as a colorless solid.

14 ¹H NMR (d₆-acetone) δ: 8.05 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz),
15 7.32 (3H, m), 3.73 (2H, s), 2.59 (2H, q, J = 7.3 Hz), 2.35 (3H, s), 1.83 (1H,
16 m), 1.05 (3H, t, J = 7.3 Hz), 0.38 (2H, m), 0.27 (2H, m).

17 (4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-
18 phenyl)-acetic acid (**Compound 131, General Formula 6**)

19 Using General Procedure I; a solution of methyl (4-{4-[(cyclopropyl-
20 ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetate (**Compound**
21 **129**, 140.0 mg, 0.39 mmol) in ethanol (5 mL) and tetrahydrofuran (5 mL)
22 was treated with NaOH (360.0 mg, 9.0 mmols, 3.0 mL of a 3N aqueous
23 solution) and stirred overnight at room temperature. Work-up followed by
24 HPLC (Partisil-10 pac 10% H₂O-CH₃CN) afforded the title compound.

25 ¹H NMR (CDCl₃) δ: 7.45 (2H, d, J = 8.2 Hz), 7.25 (5H, m), 4.16 (2H, m),
26 3.82 (2H, s), 3.56 (2H, s), 2.75 (2H, q, J = 7.3 Hz), 2.30 (3H, s), 1.86 (1H,
27 m), 1.14 (3H, t, J = 7.3 Hz), 0.54 (2H, m), 0.46 (2H, m).

1 Ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-phenylethynyl)}-benzoate
2 **(Compound 132, General Formula 6)**

3 A solution of ethyl [4-(4-bromomethyl-3-isopropyl-phenylethynyl)-
4 benzoate (**Intermediate 155**, 110.0 mg, 0.29 mmol) and cyclopropylamine
5 (420.0 mg, 7.4 mmols) in EtOH (5 mL) was stirred at 25 °C for 6 hours and
6 then concentrated under reduced pressure. The residue was dissolved in
7 EtOAc and washed with saturated aqueous NaHCO₃, H₂O and saturated
8 aqueous NaCl. The solution was dried (MgSO₄) and concentrated under
9 reduced pressure to give 103 mg (99%) of the title compound as an orange
10 oil.

11 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.5 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.47
12 (1H, s), 7.30 (2H, m), 4.38 (2H, q, J = 7.1 Hz), 3.89 (2H, s), 3.26 (1H,
13 septet, J = 7.0 Hz), 2.17 (1H, m), 1.40 (3H, t, J = 7.1 Hz), 1.26 (6H, d, J =
14 7.0 Hz), 0.45 (2H, m), 0.39 (2H, m).

15 Ethyl 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-
16 benzoate (**Compound 133, General Formula 6**)

17 To a solution of ethyl {4-(4-cyclopropylaminomethyl-3-isopropyl-
18 phenylethynyl)}-benzoate (**Compound 132**, 103.0 mg, 0.29 mmol) in 6 mL
19 of acetone was added ethyl iodide (67.0 mg, 0.43 mmol) and K₂CO₃ (79.0
20 mg, 0.57 mmol). The mixture was stirred at 60 °C for 6 hours, cooled to
21 room temperature and quenched by the addition of H₂O. The mixture was
22 extracted with EtOAc and the combined organic layers were washed with
23 H₂O and saturated aqueous NaCl before being dried (MgSO₄) and
24 concentrated under reduced pressure. Column chromatography (4-5%
25 EtOAc - hexanes) afforded 68.0 mg (59%) of the title compound.
26 ¹H NMR (CDCl₃) δ: 8.01 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 7.44
27 (1H, s), 7.28 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 3.73 (2H, s), 3.55 (1H,

1 septet, J = 6.6 Hz), 2.57 (2H, q, J = 7.3 Hz), 1.75 (1H, m), 1.40 (3H, t, J =
2 7.1 Hz), 1.22 (6H, d, J = 6.6 Hz), 1.05 (3H, t, J = 7.3 Hz), 0.37 (2H, m), 0.28
3 (2H, m).

4 4-{4-[(Cyclopropyl-ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-
5 benzoic acid (Compound 134, General Formula 6)

6 Using General Procedure I; a solution of ethyl 4-{4-[(cyclopropyl-
7 ethyl-amino)-methyl]-3-isopropyl-phenylethynyl}-benzoate (Compound
8 133, 68.0 mg, 0.17 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
9 treated with NaOH (600.0 mg, 15.0 mmols, 3.0 mL of a 5N aqueous
10 solution) and stirred overnight at room temperature and then at 55 °C for 9
11 hours. Work-up followed by crystallization of the solid residue from hot
12 CH₃CN afforded 45.0 mg (72%) of the title compound as a pale-yellow
13 solid.

14 ¹H NMR (d₆-acetone) δ: 8.05 (2H, d, J = 8.1 Hz), 7.66 (2H, d, J = 8.1 Hz),
15 7.49 (1H, s), 7.32 (2H, m), 3.78 (2H, s), 3.44 (1H, septet, J = 6.7 Hz), 2.59
16 (2H, q, J = 7.3 Hz), 1.80 (1H, m), 1.21 (6H, d, J = 6.7 Hz), 1.05 (3H, t, J =
17 7.3 Hz), 0.40 (2H, m), 0.26 (2H, m).

18 Methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
19 phenyl]-acetate (Compound 4, General Formula 8)

20 Using General Procedure F; 6-ethynyl-4,4-dimethyl-3,4-dihydro-2H-
21 naphthalen-1-one (Intermediate 13, 190.0 mg, 0.96 mmol) and methyl-(4-
22 iodophenyl)-acetate (Reagent B, 245.0 mg, 0.96 mmol) in triethyl amine (8
23 mL) was treated with copper(I)iodide (46 mg, 0.24 mmol) and sparged with
24 argon for 15 minutes. Dichlorobis(triphenylphosphine)palladium(II) (168
25 mg, 0.24 mmol) was added and the reaction mixture was stirred overnight at
26 room temperature. Column chromatography (10-20% EtOAc - hexanes)
27 afforded 250.0 mg (75%) of the title compound as a pale-yellow solid.

1 ¹H NMR (CDCl₃) δ: 7.99 (1H, d, J = 7.9 Hz), 7.57 (1H, d, J = 1.5 Hz), 7.51
2 (2H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 1.5, 7.9 Hz), 7.29 (2H, d, J = 8.5 Hz),
3 3.70 (3H, s), 3.65 (2H, s), 2.73 (2H, t, J = 7.0 Hz), 2.04 (2H, t, J = 7.0 Hz),
4 1.41 (6H, s).

5 Methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-
6 ethynyl)-phenyl]-acetate (Compound 135, General Formula 4)

7 To a solution of methyl [4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-
8 naphthalen-2-yl-ethynyl)-phenyl]-acetate (Compound 4) in 5 mL MeOH at
9 0 °C was added NaBH₄ (18.0 mg, 0.48 mmol). The reaction was stirred at 0
10 °C for 2 hours and then quenched by the addition of H₂O. The solution was
11 diluted with Et₂O and washed with H₂O and saturated aqueous NaCl before
12 being dried (MgSO₄) and the solvents were removed under reduced pressure.
13 Column chromatography (20-40% EtOAc-hexanes) afforded 140.0 mg
14 (87%) of the title compound as a colorless oil.

15 ¹H NMR (CDCl₃) δ: 7.49 (3H, m), 7.39 (1H, d, J = 7.9 Hz), 7.31 (1H, dd, J =
16 1.5, 7.9 Hz), 7.25 (2H, d, J = 8.2 Hz), 4.58 (1H, bs), 3.68 (3H, s), 3.62 (2H,
17 s), 2.05 (1H, m), 1.79 (2H, m), 1.60 (1H, m), 1.33 (3H, s), 1.26 (3H, s).

18 Methyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-
19 ylethynyl)-phenyl]-acetate (Compound 136, General Formula 4)

20 A solution of methyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-
21 naphthalen-2-ylethynyl)-phenyl]-acetate (Compound 135, 140.0 mg, 0.40
22 mmol) and carbonyldiimidazole (136.0 mg, 0.84 mmol) in 5 mL THF was
23 heated to 65 °C for 48 hours. The solution was cooled to room temperature
24 and concentrated under reduced pressure. The residue was dissolved in Et₂O
25 and washed with 5% aqueous NaOH, H₂O, and saturated aqueous NaCl
26 before being dried (Na₂SO₄) and concentrated under reduced pressure.
27 Column chromatography (5% MeOH-CH₂Cl₂) afforded 50.0 mg (31%) of

1 the title compound as a colorless solid.

2 ¹H NMR (CDCl₃) δ: 7.57 (1H, d, J = 1.5 Hz), 7.52-7.45 (3H, m), 7.27 (3H,
3 m), 7.08 (1H, s), 6.81 (2H, m), 5.30 (1H, t, J = 5.8 Hz), 3.71 (3H, s), 3.65
4 (2H, s), 2.20 (2H, m), 1.75 (2H, m), 1.40 (3H, s), 1.36 (3H, s).

5 [4-(5-Imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-
6 ethynyl)-phenyl]-acetic acid (Compound 137, General Formula 4)

7 Using General Procedure I; a solution of methyl [4-(5-imidazol-1-yl-
8 8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-phenyl]-acetate
9 (Compound 136, 50.0 mg, 0.13 mmol) in ethanol (4 mL) was treated with
10 NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred
11 overnight at room temperature. Work-up afforded 40.0 mg (83%) of the title
12 compound as a pale-orange solid.

13 ¹H NMR (d₄-MeOH) δ: 8.93 (1H, s), 7.68 (1H, s), 7.61 (1H, s), 7.54 (1H, s),
14 7.47 (2H, d, J = 8.2 Hz), 7.31 (3H, m), 6.95 (1H, d, J = 8.2 Hz), 5.83 (1H, t, J
15 = 5.8 Hz), 3.68 (1H, s), 3.63 (1H, s), 2.38 (1H, m), 2.26 (1H, m), 1.76 (2H,
16 m), 1.45 (3H, s), 1.36 (3H, s).

17 Ethyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-
18 ethynyl)-benzoate (Compound 138, General Formula 4)

19 A solution of ethyl [4-(5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-
20 naphthalen-2-yl-ethynyl)-benzoate (180.0 mg, 0.52 mmol) and
21 carbonyldiimidazole (176.0 mg, 1.08 mmol) in 5 mL THF was heated to 65
22 °C for 21 hours. The solution was cooled to room temperature and
23 concentrated under reduced pressure. The residue was dissolved in Et₂O and
24 washed with 55 aqueous NaOH, H₂O, and saturated aqueous NaCl before
25 being dried (Na₂SO₄) and concentrated under reduced pressure. Column
26 chromatography (5% MeOH-CH₂Cl₂) afforded 50.0 mg (24%) of the title
27 compound as a colorless solid.

¹H NMR (CDCl₃) δ: 8.03 (2H, d, J = 7.9 Hz), 7.59 (3H, m), 7.46 (1H, s), 7.29 (1H, dd, J = 1.5, 8.3 Hz), 7.09 (1H, s), 6.82 (1H, d, J = 8.2 Hz), 6.81 (1H, s), 5.31 (1H, t, J = 5.8 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.20 (2H, m), 1.75 (2H, m), 1.40 (9H, m).

[4-(5-Imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoic acid (Compound 139, General Formula 4)

Using General Procedure I; a solution of ethyl [4-(5-imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoate (Compound 138, 50.0 mg, 0.13 mmol) in ethanol (3 mL) and tetrahydrofuran (1 mL) was treated with NaOH (120.0 mg, 3.0 mmols, 3.0 mL of a 1N aqueous solution) and stirred overnight at room temperature. Work-up afforded 40.0 mg (87%) of the title compound as a colorless solid. ¹H NMR (d₄-MeOH) δ: 8.92 (1H, s), 8.04 (2H, d, J = 8.2 Hz), 7.74 (1H, d, J = 1.5 Hz), 7.62 (3H, m), 7.57 (1H, t, J = 1.5 Hz), 7.38 (1H, dd, J = 1.5, 7.9 Hz), 6.97 (1H, d, J = 7.9 Hz), 5.83 (1H, t, J = 5.8 Hz), 2.33 (2H, m), 1.78 (2H, m), 1.47 (3H, s), 1.39 (3H, s).

2-Isopropyl-4-trifluoromethanesulfonyloxy-benzyl acetate (Intermediate 162)

To a solution of 4-hydroxymethyl-3-isopropylphenyl 1,1,1-trifluoromethanesulfonate (Intermediate 149, 190.0 mg, 0.64 mmol) in 5 mL CH₂Cl₂ was added acetyl chloride (75.0 mg, 0.96 mmol) and pyridine (101.0 mg, 1.38 mmols). After stirring for 3 hours at 25 °C the reaction was quenched by the addition of H₂O and the resulting mixture extracted with EtOAc. The combined organic layers were washed with H₂O and saturated aqueous NaCl, dried (MgSO₄) and concentrated under reduced pressure. The title compound, 182 mg (84%), was isolated from the residual oil by column chromatography (5 - 10% EtOAc-hexanes) as a colorless oil.

1 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 8.7 Hz), 7.19 (1H, d, J = 2.7 Hz), 7.09
2 (1H, dd, J = 2.7, 8.5 Hz), 5.17 (2H, s), 3.18 (1H, septet, J = 6.7 Hz), 2.10
3 (3H, s), 1.26 (6H, d, J = 6.7 Hz).

4 4-Isopropenyloxymethyl-3-isopropyl-phenyl 1,1,1-
5 trifluoromethanesulfonate (Intermediate 163)

6 Using General Procedure 1; 2-isopropyl-4-
7 trifluoromethanesulfonyloxy-benzyl acetate (**Intermediate 162**, 182.0 mg,
8 0.54 mmols), and 1.1 mL of Tebbe's Reagent (159.0 mg, 0.56 mmols)
9 afforded 130.0 mg (72%) of the title compound as a colorless oil after
10 column chromatography (2-5% EtOAc-hexanes).

11 ¹H NMR (CDCl₃) δ: 7.43 (1H, d, J = 8.5 Hz), 7.18 (1H, d, J = 2.6 Hz), 7.09
12 (1H, dd, J = 2.6, 8.5 Hz), 4.75 (2H, s), 3.98 (2H, s), 3.12 (1H, septet, J = 6.7
13 Hz), 1.88 (3H, s), 1.25 (6H, d, J = Hz).

14 3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenyl 1,1,1-
15 trifluoromethanesulfonate (Intermediate 164)

16 Using General Procedure 2; 4-isopropenyloxymethyl-3-
17 isopropylphenyl 1,1,1-trifluoromethanesulfonate (**Intermediate 163**, 130.0
18 mg, 0.39 mmol), Et₂Zn (272.0 mg, 2.2 mmols), and CH₂I₂ (702.0 mg, 2.6
19 mmols) in 3.0 mL Et₂O afforded 120.0 mg (89%) of the title compound as a
20 colorless oil after column chromatography (4-5% EtOAc - hexanes).

21 ¹H NMR (CDCl₃) δ: 7.39 (1H, d, J = 8.5 Hz), 7.13 (1H, d, J = 2.7 Hz), 7.05
22 (1H, dd, J = 2.7, 8.5 Hz), 4.54 (2H, s), 3.16 (1H, septet, J = 6.7 Hz), 1.47
23 (3H, s), 1.24 (6H, d, J = 6.7 Hz), 0.86 (2H, m), 0.48 (2H, m).

24 [3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-
25 trimethylsilane (Intermediate 165)

26 Using General Procedure D; 3-isopropyl-4-(1-methyl-
27 cyclopropoxymethyl)-phenyl 1,1,1-trifluoromethanesulfonate (**Intermediate**

1 164, 120.0 mg, 0.34mmol) in triethylamine (2 mL) and anhydrous DMF (5
2 mL) was sparged with argon for 5 minutes. Trimethylsilyl acetylene (700.0
3 mg, 0.71 mmol) was then added followed by
4 dichlorobis(triphenylphosphine)palladium(II) (24.0 mg, 0.03 mmol). The
5 resulting reaction mixture was heated to 95 °C for 60 hours. The title
6 compound 110.0 mg, (99%) was isolated by chromatography (0-1% EtOAc
7 - hexanes).

8 ¹H NMR (CDCl₃) δ: 7.36 (1H, s), 7.24 (2H, bs), 4.53 (2H, s), 3.11 (1H,
9 septet, J = 6.7 Hz), 1.45 (3H, s), 1.22 (6H, d, J = 6.7 Hz), 0.85 (2H, m), 0.44
10 (2H, m), 0.25 (9H, s).

11 4-Ethynyl-2-isopropyl-1-(1-methyl-cyclopropoxymethyl)-benzene
12 **(Intermediate 166)**

13 Using General Procedure E; [3-isopropyl-4-(1-methyl-
14 cyclopropoxymethyl)-phenylethynyl]-trimethylsilane (**Intermediate 165**,
15 110.0 mg, 0.37 mmol) in methanol (6 mL) was treated with potassium
16 carbonate (80.0 mg, 0.58 mmol) and stirred overnight at ambient
17 temperature. The crude alkyne (84 mg, 100%) was used directly in the next
18 reaction.

19 ¹H NMR (CDCl₃) δ: 7.55 (1H, s), 7.41 (2H, m), 4.68 (2H, s), 3.26 (1H,
20 septet, J = 6.8 Hz), 3.18 (1H, s), 1.60 (3H, s), 1.37 (6H, d, J = 6.8 Hz), 0.99
21 (2H, m), 0.59 (2H, m).

22 Methyl {4-[3-isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-
23 phenyl}-acetate (**Compound 140, General Formula 6**)

24 Using General Procedure F; 4-ethynyl-2-isopropyl-1-(1-methyl-
25 cyclopropoxymethyl)-benzene (**Intermediate 166**, 78.0 mg, 0.34 mmol) and
26 methyl-(4-iodophenyl)-acetate (**Reagent B**, 94.0 mg, 0.34 mmol) in
27 triethylamine (8 mL) was treated with copper(I)iodide (22.0 mg, 0.11 mmol)

1 and sparged with argon for 5 minutes.
2 Dichlorobis(triphenylphosphine)palladium(II) (79 mg, 0.11 mmol) was
3 added and the reaction mixture was stirred at room temperature for 3.5
4 hours. Column chromatography (2-5% EtOAc - hexanes) afforded 77.0 mg
5 (60%) of the title compound as a yellow oil.

6 ¹H NMR (CDCl₃) δ: 7.49 (2H, d, J = 8.2 Hz), 7.43 (1H, d, J = 1.5 Hz), 7.33-
7 7.24 (4H, m), 4.55 (2H, s), 3.70 (3H, s), 3.63 (2H, s), 3.14 (1H, septet, J =
8 6.8 Hz), 1.47 (3H, s), 1.25 (6H, d, J = 6.8 Hz), 0.86 (2H, m), 0.46 (2H, m).

9 4-[3-Isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-
10 acetic acid (Compound 141, Formula 6)

11 Using General Procedure I; a solution methyl {4-[3-isopropyl-4-(1-
12 methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetate (**Compound**
13 **140**, 70.0 mg, 0.19 mmol) in ethanol (3 mL) and tetrahydrofuran (3 mL) was
14 treated with NaOH (240.0 mg, 6.0 mmols, 2.0 mL of a 3N aqueous solution)
15 and stirred overnight at room temperature. Work-up and purification by
16 HPLC (Partisil 10-pac, 10% H₂O/CH₃CN) afforded of the title compound as
17 a colorless solid.

18 ¹H NMR (CDCl₃) δ: 7.50 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.33-7.24 (4H,
19 m), 4.55 (2H, s), 3.65 (2H, s), 3.14 (1H, septet, J = 6.7 Hz), 1.47 (3H, s),
20 1.25 (6H, d, J = 6.7 Hz), 0.87 (2H, m), 0.46 (2H, m).

21 2,6-Di-*tert*-butyl-4-trimethylsilanylethynyl-phenol: (Intermediate 167)

22 Following General Procedure D and using 4-bromo-2,6-di-*t*-butyl-
23 phenol (1.43g, 5mmol), triethyl amine (15mL), anhydrous tetrahydrofuran
24 (15mL), copper(I)iodide (0.06g, 0.31mmol), trimethylsilyl acetylene (4.9g,
25 50mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.18g,
26 0.26mmol) followed by flash column chromatography over silica gel (230-
27 400 mesh) using hexane as eluent, the title compound was obtained (1.35g,

1 90%).

2 ¹H NMR (300 MHz, CDCl₃): δ 7.29 (s, 2H), 5.35 (s, 1H), 1.42 (s, 18H), 0.24
3 (s, 9H).

4 (3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-trimethyl-silane:

5 **(Intermediate 168)**

6 A solution 2,6-di-*tert*-butyl-4-trimethylsilanylethynyl-phenol
7 **(Intermediate 167, 0.302g, 1mmol)** in acetone (5mL) was treated with
8 potassium carbonate (0.138g, 1mmol) and methyl iodide (0.142g, 1mmol)
9 and stirred overnight at room temperature. The volatiles were distilled off *in*
10 *vacuo* and the residue was purified by flash column chromatography on
11 silica gel (230-400 mesh) using ethyl acetate as the eluent to afford the title
12 compound as a white solid (0.28g, 90%).

13 ¹H NMR (300 MHz, CDCl₃): δ 7.41 (s, 2H), 3.70 (s, 3H), 1.49 (s, 18H), 0.30
14 (s, 9H).

15 1,3-Di-*tert*-butyl-5-ethynyl-2-methoxy-benzene: (Intermediate 169)

16 Following General Procedure E and (3,5-di-*tert*-butyl-4-methoxy-
17 phenylethynyl)-trimethyl-silane **(Intermediate 168, 0.28g, 0.9mmol)**,
18 potassium carbonate (0.98g, 7.1mmol) and methanol (10mL) followed by
19 flash column chromatography over silica gel (230-400 mesh) using hexane
20 as the eluent, the title compound was obtained (0.23g, 100%).

21 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (s, 2H), 3.75 (s, 3H), 3.05 (s, 1H), 1.49
22 (s, 18H).

23 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid methyl
24 ester: (Compound 142, General Formula 5)

25 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-
26 2-methoxy-benzene **(Intermediate 169, 0.094g, 0.36mmol)**, methyl-4-iodo
27 phenyl acetate **(Reagent B, 0.09g, 0.32mmol)**, triethyl amine (5mL),

1 anhydrous tetrahydrofuran (5mL), copper(I)iodide (0.02g, 0.1mmol) and
2 dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol) followed
3 by flash column chromatography over silica gel (230-400 mesh) using 10 %
4 ethyl acetate in hexane as the eluent, the title compound (0.114g, 81%) was
5 obtained as an oil.

6 ¹H NMR (300 MHz, CDCl₃): δ 7.52 (d, 2H, *J* = 8.0Hz), 7.46 (s, 2H), 7.28 (d,
7 2H, *J* = 8.2Hz), 3.72 (s, 3H), 3.71(s, 3H), 3.66 (s, 2H), 1.47 (s, 18H).

8 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-phenyl]-acetic acid:

9 **(Compound 143, General Formula 5)**

10 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-
11 methoxy-phenylethynyl)-phenyl]-acetic acid methyl ester (**Compound 142**,
12 0.114g, 0.29mmol), 5M aqueous sodium hydroxide solution (2mL) and
13 ethanol (4mL), followed by preparative reverse phase HPLC using 10%
14 water in acetonitrile as the mobile phase, the title compound was obtained as
15 a white solid (0.097g, 88%).

16 ¹H NMR (300 MHz, CDCl₃): δ 7.55(d, 2H, *J* = 8.0Hz), 7.48 (s, 2H), 7.30 (d,
17 2H, *J* = 8.2Hz), 3.74 (s, 3H), 3.69 (s, 2H), 1.49 (s, 18H).

18 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid

19 methyl ester: (Compound 144, General Formula 5)

20 Following General Procedure F and using 1,3-di-*tert*-butyl-5-ethynyl-
21 2-methoxy-benzene (**Intermediate 169**, 0.087g, 0.33mmol), methyl-2-
22 fluoro-4-iodo phenyl acetate (**Reagent H**, 0.088g, 0.30mmol), triethyl amine
23 (5mL), anhydrous tetrahydrofuran (10mL), copper(I)iodide (0.02g, 0.1mmol)
24 and dichlorobis(triphenylphosphine)palladium(II) (0.06g, 0.085mmol)
25 followed by flash column chromatography over silica gel (230-400 mesh)
26 using 10 % ethyl acetate in hexane as the eluent, the title compound (0.122g,
27 89%) was obtained.

1 ¹H NMR (300 MHz, CDCl₃): δ 7.46 (s, 2H), 7.33-7.24 (m, 3H), 3.75 (s, 3H),
2 3.73(s, 3H), 3.72 (s, 2H), 1.48 (s, 18H).

3 [4-(3,5-Di-*tert*-butyl-4-methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic
4 acid: (Compound 145, General Formula 5)

5 Following General Procedure I and using [4-(3,5-di-*tert*-butyl-4-
6 methoxy-phenylethynyl)-2-fluoro-phenyl]-acetic acid methyl ester
7 (Compound 144, 0.122g, 0.29mmol), 5M aqueous sodium hydroxide
8 solution (1mL) and ethanol (4mL), followed preparative reverse phase
9 HPLC using 10% water in acetonitrile as the mobile phase, the title
10 compound was obtained as a white solid (0.077g, 65%).
11 ¹H NMR (300 MHz, CDCl₃): δ 7.42 (s, 2H), 7.29-7.19 (m, 3H), 3.71 (s, 2H),
12 3.69 (s, 3H), 1.43 (s, 18H).

1 WHAT IS CLAIMED IS:

2 1. A compound of the formula

3

4

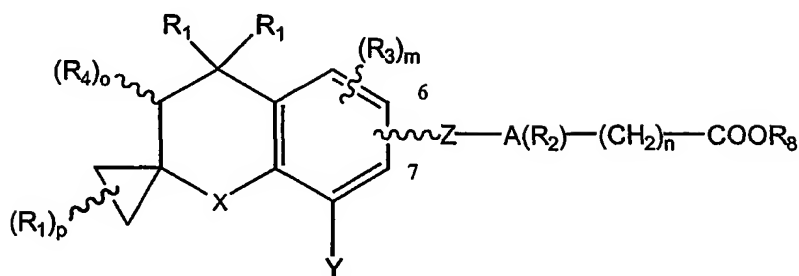
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10 wherein A is a phenyl or naphthyl group, or heteroaryl selected from

11 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,

12 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and

13 heteroaryl groups being optionally substituted with one or two R_2 groups;

14 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;

15 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen

16 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of

17 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,

18 or I;

19 Z is $-C\equiv C-$,20 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,21 $-CO-NR_1-$,22 NR_1-CO- ;23 $-CO-O-$,24 $-O-CO-$,25 $-CS-NR_1-$,26 NR_1-CS- ,27 $-CO-S-$,

- 1 -S-CO-,
2 -N=N-;
- 3 **R₁** is independently H or alkyl of 1 to 6 carbons;
4 **p** is an integer having the values of 0 to 4;
5 **R₂** is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃,
6 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
7 alkylthio of 1 to 6 carbons;
8 **R₃** is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
9 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
10 alkylthio of 1 to 6 carbons or benzyl;
11 **m** is an integer having the values 0 to 2;
12 **R₄** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
13 alkyl of 1 to 6 carbons, or halogen;
14 **o** is an integer having the values of 0 to 2;
15 **n** is an integer having the values of 0 to 4, and
16 **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
17 pharmaceutically acceptable base.
- 18 **2.** A compound in accordance with Claim 1 where A is phenyl,
19 naphthyl, pyridyl, thienyl or furyl.
- 20 **3.** A compound in accordance with Claim 1 where **n** is 0, 1 or 2.
- 21 **4.** A compound in accordance with Claim 1 where Z is -C≡C-, -CO-
22 NR₁-,
23 -CO-O-, or -(CR₁=CR₁)_n, where **n'** is 1.
- 24 **5.** A compound in accordance with Claim 1 where the Z group is
25 attached to the 6-position of the bicyclic moiety.
- 26 **6.** A compound in accordance with Claim 1 where X is O.
- 27 **7.** A compound in accordance with Claim 1 where Y is H, lower

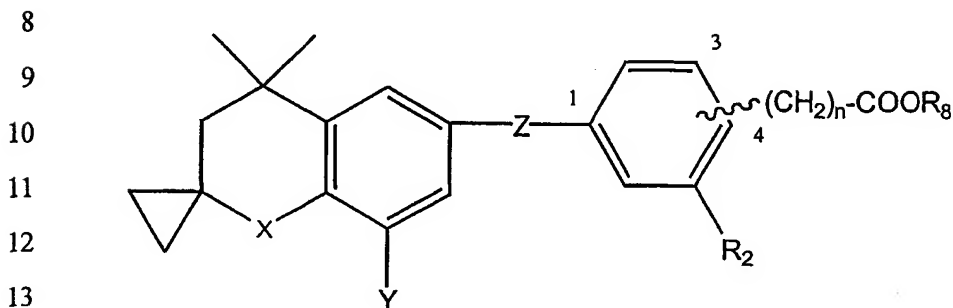
1 alkyl of 1 to 3 carbons or cyclopropyl.

2 8. A compound in accordance with Claim 1 where A is phenyl.

3 9. A compound in accordance with Claim 8 where Z is $-C\equiv C-$, or -
4 CO-O-.

5 10. A compound in accordance with Claim 9 where Y is H or
6 cyclopropyl.

7 11. A compound of the formula



15 where X is O or CH_3N ;

16 Y is H or cyclopropyl;

17 Z is $-C\equiv C-$ or $-CO-O-$;

18 R_2 is H or F;

19 n is 0 or 1, and

20 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
21 acceptable base.

22 12. A compound in accordance with Claim 11 where X is O.

23 13. A compound in accordance with Claim 12 where Y is H and Z is
24 $-C\equiv C-$.

25 14. A compound in accordance with Claim 13 where the -
26 $(CH_2)_nCOOR_8$ group is in the 4 position of the phenyl ring.

27 15. A compound in accordance with Claim 14, which is selected
28 from the group consisting of:

1 benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-
2 2,1'-cyclopropane]-6-yl)ethynyl]-, benzeneacetic acid, 4-[(3,4-dihydro-4,4-
3 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]- and 2-
4 fluoro-benzoic acid, 4-[(3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-
5 2,1'-cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically
6 acceptable base or a C₁₋₆ alkyl ester of said compound.

7 **16.** A compound in accordance with Claim 12 where Y is
8 cyclopropyl and Z is -C≡C-.

9 **17.** A compound in accordance with Claim 16 where the -
10 (CH₂)_nCOOR₈ group is in the 4 position of the phenyl ring.

11 **18.** A compound in accordance with Claim 17, which is selected
12 from the group consisting of:

13 benzeneacetic acid, 4-[(8-cyclopropyl-3,4-dihydro-4,4-
14 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-, 4-[(8-
15 cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
16 cyclopropane]-6-yl)ethynyl]-2-fluoro-benzeneacetic acid, benzoic acid, 4-
17 [(8-cyclopropyl-3,4-dihydro-4,4-dimethylspiro[2*H*-1-benzopyran-2,1'-
18 cyclopropane]-6-yl)ethynyl]- and 4-[(8-cyclopropyl-3,4-dihydro-4,4-
19 dimethylspiro[2*H*-1-benzopyran-2,1'-cyclopropane]-6-yl)ethynyl]-2-fluoro-
20 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
21 ester of said compound.

22 **19.** A compound in accordance with Claim 12 where Y is
23 cyclopropyl and Z is -CO-O-.

24 **20.** A compound in accordance with Claim 19 where the -
25 (CH₂)_nCOOR₈ group is in the 4 position of the phenyl ring.

26 **21.** A compound in accordance with Claim 20 which is spiro[2*H*-1-
27 benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-3,4-
28 dihydro-4,4-dimethyl-, 4-(carboxymethyl)phenyl ester or a salt with a

1 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

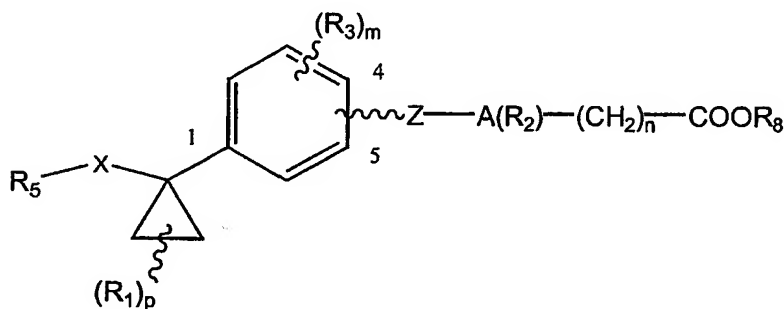
2 22. A compound in accordance with Claim 19 where the -
3 (CH₂)_nCOOR₈ group is in the 3 position of the phenyl ring.

4 23. A compound in accordance with Claim 22 which is spiro[2*H*-1-
5 benzopyran-2,1'-cyclopropane]-6-carboxylic acid, 8-cyclopropyl-3,4-
6 dihydro-4,4-dimethyl-, 3-(carboxymethyl)phenyl ester or a salt with a
7 pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said compound.

8 24. A compound in accordance with Claim 11 where X is CH₃N, Y
9 is H and Z is -C≡C-.

10 25. A compound in accordance with Claim 22 which is benzoic acid,
11 4-[(1,4,4-trimethylspiro[2*H*-1-1,2,3,4-tetrahydroquinoline-2,1'-
12 cyclopropane]-6-yl)ethynyl]- or a salt with a pharmaceutically acceptable
13 base or a C₁₋₆ alkyl ester of said compound.

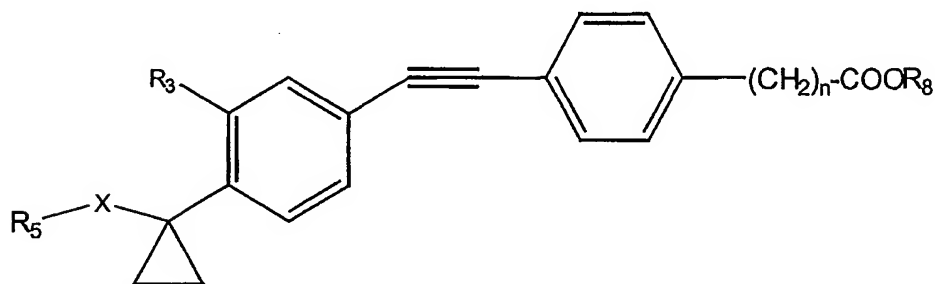
14 26. A compound of the formula



22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
25 heteroaryl groups being optionally substituted with one or two R₂ groups;
26

- 1 X is O, S or NR where R is H, alkyl of 1 to 6 carbons or benzyl;
2 Z is $-C\equiv C-$,
3 $-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,
4 $-CO-NR_1-$,
5 NR_1-CO- ,
6 $-CO-O-$,
7 $-O-CO-$,
8 $-CS-NR_1-$,
9 NR_1-CS- ,
10 $-CO-S-$,
11 $-S-CO-$,
12 $-N=N-$;
13 R_1 is independently H or alkyl of 1 to 6 carbons;
14 p is an integer having the values of 0 to 4;
15 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
16 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
17 to 6 carbons;
18 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
19 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
20 alkylthio of 1 to 6 carbons or benzyl;
21 m is an integer having the values 0 to 4;
22 R_5 is H, alkyl of 1 to 6 carbons, fluorosubstituted alkyl of 1 to 6
23 carbons, benzyl, or lower alkyl or halogen substituted benzyl;
24 n is an integer having the values of 0 to 4, and
25 R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}\text{-alkyl})$, or a cation of a
26 pharmaceutically acceptable base.
27 27. A compound in accordance with Claim 26 where A is phenyl,
28 naphthyl, pyridyl, thienyl or furyl.

- 1 28. A compound in accordance with Claim 26 where n is 0, 1 or 2.
 2 29. A compound in accordance with Claim 26 where Z is $-C\equiv C-$, -
 3 $CO-NR_1-$, $-CO-O-$, or $-(CR_1=CR_1)_n$, where n' is 1.
 4 30. A compound in accordance with Claim 26 where the Z group is
 5 attached to the 4-position of the phenyl moiety.
 6 31. A compound in accordance with Claim 26 where X is O.
 7 32. A compound in accordance with Claim 26 where X is NR.
 8 33. A compound of the formula



- 9 where X is O, NR where R is H, n -propyl or benzyl;
 10 R_3 is H or lower alkyl of 1 to 6 carbons;
 11 R_5 is benzyl or lower alkyl of 1 to 6 carbons;
 12 n is 0 or 1, and
 13 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
 14 acceptable base.
 15 34. A compound in accordance with Claim 33 where X is NR.
 16 35. A compound in accordance with Claim 34 where R is n -propyl
 17 and R_5 is n -propyl.
 18 36. A compound in accordance with Claim 35 which is 4-[4-(1-
 19 dipropylamino-cyclopropyl)-phenylethynyl]-benzoic acid or a salt with a
 20 pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.
 21 37. A compound in accordance with Claim 34 where R is H and R_5

1 is *n*-propyl or benzyl.

2 38. A compound in accordance with Claim 37 which is selected from
3 the group consisting of 4-[4-(1-propylamino-cyclopropyl)-phenylethynyl]-
4 benzoic acid and 4-[4-(1-benzylamino-cyclopropyl)-phenylethynyl]-benzoic
5 acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of
6 said compound.

7 39. A compound in accordance with Claim 34 where R is benzyl or
8 methyl and R₅ is benzyl.

9 40. A compound in accordance with Claim 39 which is selected from
10 the group consisting of 4-[4-(1-dibenzylamino-cyclopropyl)-
11 phenylethynyl]-benzoic acid and 4-[4-(1-benzylmethylamino-cyclopropyl)-
12 phenylethynyl]-benzoic acid or a salt with a pharmaceutically acceptable
13 base or a C₁₋₆ alkyl ester of said compound.

14 41. A compound in accordance with Claim 33 where X is O.

15 42. A compound in accordance with Claim 41 where R₅ is benzyl
16 and *n* is 0.

17 43. A compound in accordance with Claim 42 which is selected from
18 the group consisting of 4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-
19 benzoic acid, 4-[4-(1-benzyloxycyclopropyl)-3-methyl-phenylethynyl]-
20 benzoic acid and 4-[4-(1-benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-
21 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆
22 alkyl ester of said compound.

23 44. A compound in accordance with Claim 41 where R₅ is benzyl
24 and *n* is 1.

25 45. A compound in accordance with Claim 44 which is selected from
26 the group consisting of {4-[4-(1-benzyloxycyclopropyl)-phenylethynyl]-
27 phenyl}-acetic acid, {4-[4-(1-benzyloxycyclopropyl)-3-methyl-
28 phenylethynyl]-phenyl}-acetic acid and {4-[4-(1-benzyloxycyclopropyl)-3-

1 ethyl-phenylethynyl]-phenyl}-acetic acid or a salt with a pharmaceutically
2 acceptable base or a C₁₋₆ alkyl ester of said compound.

3 46. A compound in accordance with Claim 41 where R₅ is methyl,
4 ethyl, *iso*-propyl, or (CH₃)₃-CH₂- and n is 0.

5 47. A compound in accordance with Claim 46 which is selected from
6 the group consisting of 4-[4-(1-methoxycyclopropyl)-phenylethynyl]-
7 benzoic acid, 4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-benzoic acid,
8 4-[4-(1-isopropoxycyclopropyl)-3-methyl-phenylethynyl]-benzoic acid, 4-
9 [4-[1-(2,2-dimethylpropyloxy)-cyclopropyl]-3-methyl-phenylethynyl]-
10 benzoic acid and 4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-
11 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
12 ester of said compound.

13 48. A compound in accordance with Claim 41 where R₅ is methyl,
14 ethyl, *iso*-propyl, or (CH₃)₃-CH₂- and n is 1.

15 49. A compound in accordance with Claim 48 which is selected from
16 the group consisting of {4-[4-(1-methoxycyclopropyl)-phenylethynyl]-
17 phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-phenylethynyl]-
18 phenyl}-acetic acid, {4-[4-(1-isopropoxycyclopropyl)-3-methyl-
19 phenylethynyl]-phenyl}-acetic acid, {4-[4-[1-(2,2-dimethylpropyloxy)-
20 cyclopropyl]-3-methyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-(1-
21 benzyloxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid, {4-[4-
22 (1-isopropoxycyclopropyl)-3-ethyl-phenylethynyl]-phenyl}-acetic acid and
23 {4-[4-(1-ethoxycyclopropyl)-3-*tert*-butyl-phenylethynyl]-phenyl}-acetic acid
24 or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl ester of said
25 compound.

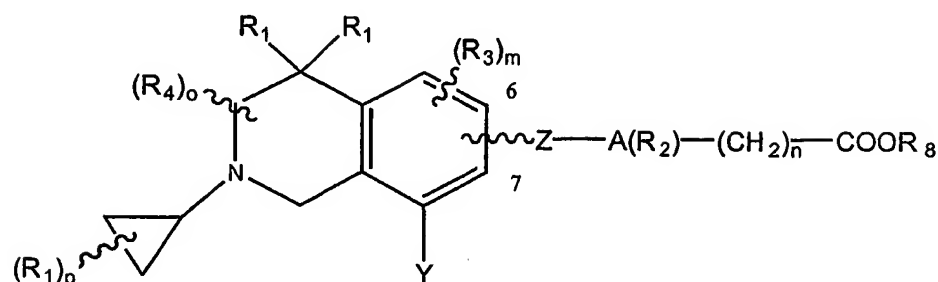
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1 **50.** A compound of the formula



2 wherein **A** is a phenyl or naphthyl group, or heteroaryl selected from
 3 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
 4 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
 5 heteroaryl groups being optionally substituted with one or two **R₂** groups;

6 **Y** is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 7 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of
 8 3 to 6 carbons, lower alkyl substituted cycloalkyl of 1 to 6 carbons, Cl, Br,
 9 or I;

10 **Z** is -C≡C-,
 11 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,
 12 -CO-NR₁-,
 13 NR₁-CO-,
 14 -CO-O-,
 15 -O-CO-,
 16 -CS-NR₁-,
 17 NR₁-CS-,
 18 -CO-S-,
 19 -S-CO-,
 20 -N=N-;

1 R_1 is independently H or alkyl of 1 to 6 carbons;

2 p is an integer having the values of 0 to 5;

3 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
4 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
5 to 6 carbons;

6 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
7 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
8 alkylthio of 1 to 6 carbons or benzyl;

9 m is an integer having the values 0 to 2;

10 R_4 is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
11 alkyl of 1 to 6 carbons, or halogen;

12 o is an integer having the values of 0 to 4;

13 n is an integer having the values of 0 to 4, and

14 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
15 pharmaceutically acceptable base.

16 **51.** A compound in accordance with Claim 50 where A is phenyl,
17 naphthyl, pyridyl, thienyl or furyl.

18 **52.** A compound in accordance with Claim 50 where n is 0, 1 or 2.

19 **53.** A compound in accordance with Claim 50 where Z is $-\text{C}\equiv\text{C}-$, -
20 $\text{CO}-\text{NR}_1-$,
21 $-\text{CO}-\text{O}-$, or $-(\text{CR}_1=\text{CR}_1)_n$, where n' is 1.

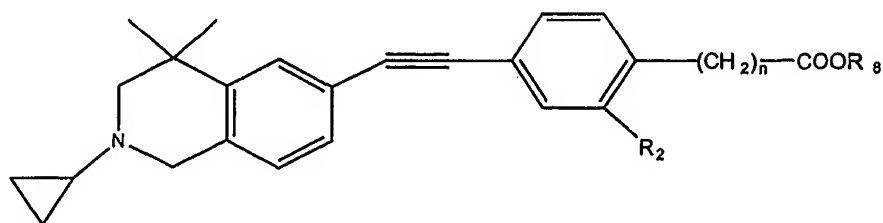
22 **54.** A compound in accordance with Claim 50 where the Z group is
23 attached to the 6-position of the bicyclic moiety.

24 **55.** A compound in accordance with Claim 50 where Y is H, lower
25 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or
26 halogen.

27 **56.** A compound in accordance with Claim 50 where A is phenyl.

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1 57. A compound of the formula



7 where R_2 is H or halogen;

8 n is 0 or 1 and

9 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
10 acceptable base.

11 58. A compound in accordance with Claim 57 where n is 1 and R_2 is

12 F.

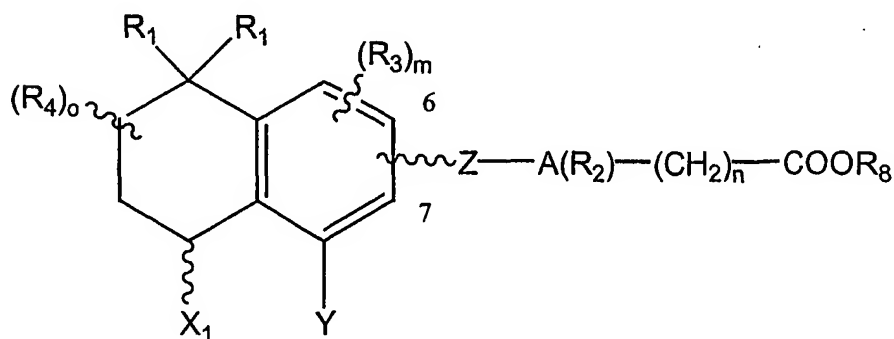
13 59. A compound in accordance with Claim 58 which is [4-(2-
14 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-2-
15 fluoro-phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

16 60. A compound in accordance with Claim 57 where n is 1 and R_2 is

17 H.

18 61. A compound in accordance with Claim 60 which is [4-(2-
19 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl-ethynyl)-
20 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base.

21 62. A compound of the formula



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
2 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and
4 heteroaryl groups being optionally substituted with one or two R_2 groups;

5 X_1 is 1-imidazolyl, or lower alkyl or halogen substituted 1-
6 imidazolyl, OR, SR, NRR_6 where R is H, alkyl of 1 to 6 carbons or benzyl;

7 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
8 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of
9 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,
10 or I;

11 Z is $-C\equiv C-$,
12 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,
13 $-CO-NR_1-$,
14 NR_1-CO- ,
15 $-CO-O-$,
16 $-O-CO-$,
17 $-CS-NR_1-$,
18 NR_1-CS- ,
19 $-CO-S-$,
20 $-S-CO-$,
21 $-N=N-$;

22 R_1 is independently H or alkyl of 1 to 6 carbons;

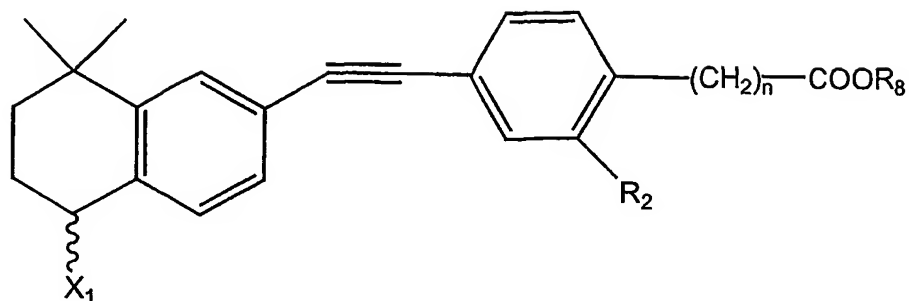
23 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
24 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
25 to 6 carbons;

26 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
27 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,

- 1 alkylthio of 1 to 6 carbons or benzyl;
2 **m** is an integer having the values 0 to 2;
3 **R₄** is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
4 alkyl of 1 to 6 carbons, or halogen;
5 **o** is an integer having the values of 0 to 4;
6 **R₆** is H, lower alkyl, cycloalkyl of 3 to 6 carbons, lower alkyl
7 substituted cycloalkyl of 3 to 6 carbons;
8 **n** is an integer having the values of 0 to 4, and
9 **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
10 pharmaceutically acceptable base, with the proviso that when **Y** is H, **A** is
11 phenyl and **X₁** is OH then **n** is 1 to 4.
- 12 **63.** A compound in accordance with Claim 62 where **A** is phenyl,
13 naphthyl, pyridyl, thienyl or furyl.
- 14 **64.** A compound in accordance with Claim 62 where **n** is 0, 1 or 2.
- 15 **65.** A compound in accordance with Claim 62 where **Z** is -C≡C-, -
16 CO-NR₁-,
17 -CO-O-, or -(CR₁=CR₁)_n, where **n'** is 1.
- 18 **66.** A compound in accordance with Claim 62 where the **Z** group is
19 attached to the 6-position of the bicyclic moiety.
- 20 **67.** A compound in accordance with Claim 62 where **X₁** is 1-
21 imidazolyl, halogen or C₁₋₆ substituted 1-imidazolyl, or NRR₆, where **R₆** is
22 preferably cyclopropyl or branched-chain alkyl of 1 to 6 carbons.
- 23 **68.** A compound in accordance with Claim 62 where **Y** is H, lower
24 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or
25 halogen.
26

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69. A compound of the formula



wherein X_1 is 1-imidazolyl, or dialkyl-N or alkyl,cyclopropyl-N

where the alkyl group has 1 to 6 carbons;

R_2 is H or halogen;

n is 0 or 1, and

R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically acceptable base.

70. A compound in accordance with Claim 69 where X_1 is methyl,cyclopropyl-N and n is 0.

71. A compound in accordance with Claim 70 which is selected from the group consisting of 4-[(5-cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-benzoic acid and 4-[5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl]-2-fluoro benzoic acid or a salt with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

72. A compound in accordance with Claim 69 where X_1 is methyl,cyclopropyl-N and n is 1.

73. A compound in accordance with Claim 72 which is selected from the group consisting of 4-[(5-(cyclopropyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [4-(5-

1 (cyclopropyl-methyl-amino)-8,8-dimethyl- 5,6,7,8-tetrahydro-naphthalene-2-
 2 yl-ethynyl)-2-fluoro-phenyl]-acetic acid or a salt with a pharmaceutically
 3 acceptable base or a C₁₋₆ alkyl ester of said compound.

4 74. A compound in accordance with Claim 69 where X₁ is
 5 methyl, *iso*-propyl-N.

6 75. A compound in accordance with Claim 74 which is 4-[5-(*iso*-
 7 propyl-methyl-amino)-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalene-2-yl-
 8 ethynyl)]-benzoic acid or a salt with a pharmaceutically acceptable base or a
 9 C₁₋₆ alkyl ester of said compound.

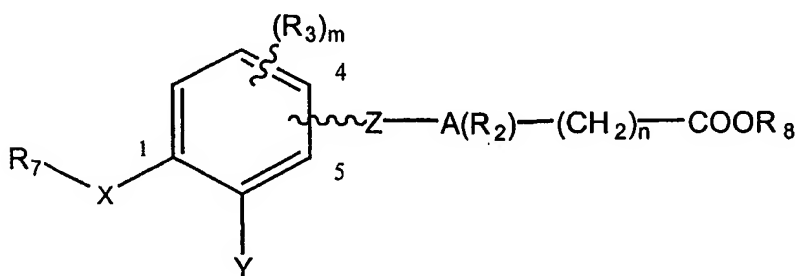
10 76. A compound in accordance with Claim 69 where X₁ is 1-
 11 imidazolyl and n is 0.

12 77. A compound in accordance with Claim 76 which is [4-(5-
 13 imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
 14 benzoic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆ alkyl
 15 ester of said compound.

16 78. A compound in accordance with Claim 69 where X₁ is 1-
 17 imidazolyl and n is 1.

18 79. A compound in accordance with Claim 78 which is [4-(5-
 19 imidazol-1-yl-8,8-dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-
 20 phenyl]-acetic acid or a salt with a pharmaceutically acceptable base or a C₁₋₆
 21 alkyl ester of said compound.

22 80. A compound of the formula



1 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
2 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
4 heteroaryl groups being optionally substituted with one or two R_2 groups;

5 X is O, S or NR where R is H, alkyl of 1 to 6 carbons, C_{1-6} -
6 trialkylsilyl or benzyl; Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl
7 or halogen substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons,
8 cycloalkyl of 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6
9 carbons, Cl, Br, or I;

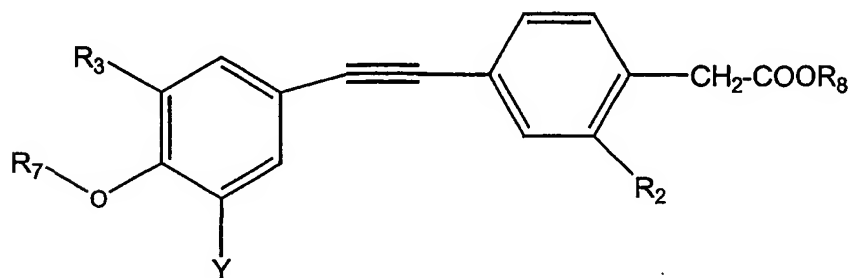
10 Z is $-C\equiv C-$,
11 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,
12 $-CO-NR_1-$,
13 NR_1-CO- ,
14 $-CO-O-$,
15 $-O-CO-$,
16 $-CS-NR_1-$,
17 NR_1-CS- ,
18 $-CO-S-$,
19 $-S-CO-$,
20 $-N=N-$;

21 R_1 is independently H or alkyl of 1 to 6 carbons;

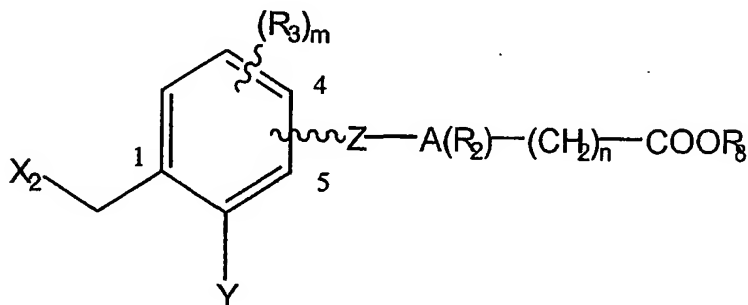
22 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
23 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
24 to 6 carbons;

25 R_3 is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
26 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
27 alkylthio of 1 to 6 carbons or benzyl;

- 1 **m** is an integer having the values 0 to 3;
- 2 **R₇** is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or lower
- 3 alkyl substituted cycloalkyl of 1 to 6 carbons;
- 4 **n** is an integer having the values of 1 to 4, and
- 5 **R₈** is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
- 6 pharmaceutically acceptable base.
- 7 **81.** A compound in accordance with Claim 80 where A is phenyl,
- 8 naphthyl, pyridyl, thienyl or furyl.
- 9 **82.** A compound in accordance with Claim 80 where **n** is 0, 1 or 2.
- 10 **83.** A compound in accordance with Claim 80 where Z is -C≡C-, -
- 11 CO-NR₁-,
- 12 -CO-O-, or -(CR₁=CR₁)_n, where **n'** is 1.
- 13 **84.** A compound in accordance with Claim 80 where the Z group is
- 14 attached to the 4-position of the phenyl moiety.
- 15 **85.** A compound in accordance with Claim 80 where X is O.
- 16 **86.** A compound in accordance with Claim 80 where Y is H, lower
- 17 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or
- 18 halogen.
- 19 **87.** A compound in accordance with Claim 80 where A is phenyl.
- 20 **88.** A compound in accordance with Claim 80 where **n** is 1.
- 21 **89.** A compound of the formula



- 1 wherein Y is branched-chain alkyl of 3 to 6 carbons;
 2 R_2 is H or F;
 3 R_3 is branched-chain alkyl of 3 to 6 carbons;
 4 R_7 is lower alkyl of 1 to 6 carbons, and
 5 R_8 is H, alkyl of 1 to 6 carbons, $-\text{CH}_2\text{O}(\text{C}_{1-6}\text{-alkyl})$, or a cation of a
 6 pharmaceutically acceptable base.
- 7 90. A compound in accordance with Claim 89 where Y is *t*-butyl.
 8 91. A compound in accordance with Claim 90 where R_3 is *t*-butyl.
 9 92. A compound in accordance with Claim 91 where R_7 is methyl.
 10 93. A compound in accordance with Claim 92 which is selected from
 11 the group consisting of [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-
 12 phenyl]-acetic acid and [4-(3,5-di-*tert*-butyl-4-methoxy-phenylethynyl)-2-
 13 fluoro-phenyl]-acetic acid or a salt of said compound with a
 14 pharmaceutically acceptable base.
- 15 94. A compound of the formula



- 23 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
 24 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
 25 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
 26 heteroaryl groups being optionally substituted with one or two R_2 groups;
 27 X_2 is 1-imidazolyl, lower alkyl or halogen substituted 1-imidazolyl,

- 1 OR_7 , SR_7 or NRR_7 where R is H, alkyl of 1 to 6 carbons or benzyl;
- 2 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
- 3 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of
- 4 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, Cl, Br,
- 5 or I;
- 6 Z is $-C\equiv C-$,
- 7 $-(CR_1=CR_1)_{n'}$, where n' is an integer having the value 1 - 5,
- 8 $-CO-NR_1-$,
- 9 NR_1-CO- ,
- 10 $-CO-O-$,
- 11 $-O-CO-$,
- 12 $-CS-NR_1-$,
- 13 NR_1-CS- ,
- 14 $-CO-S-$,
- 15 $-S-CO-$,
- 16 $-N=N-$;
- 17 R_1 is independently H or alkyl of 1 to 6 carbons;
- 18 R_2 is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
- 19 substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or alkylthio of 1
- 20 to 6 carbons;
- 21 R_3 is alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1
- 22 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, alkylthio of 1 to 6 carbons
- 23 or benzyl;
- 24 m is an integer having the values 0 to 3;
- 25 R_7 is H, alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, lower
- 26 alkyl substituted cycloalkyl of 3 to 6 carbons or C_{1-6} -trialkylsilyl.
- 27 n is an integer having the values of 0 to 4, and
- 28 R_8 is H, alkyl of 1 to 6 carbons, $-CH_2O(C_{1-6}$ -alkyl), or a cation of a

1 pharmaceutically acceptable base.

2 **95.** A compound in accordance with Claim 94 where A is phenyl,
3 naphthyl, pyridyl, thienyl or furyl.

4 **96.** A compound in accordance with Claim 94 where n is 0, 1 or 2.

5 **97.** A compound in accordance with Claim 94 where Z is $-C\equiv C-$, -
6 $CO-NR_1-$,
7 $-CO-O-$, or $-(CR_1=CR_1)_n$, where n' is 1.

8 **98.** A compound in accordance with Claim 94 where the Z group is
9 attached to the 4-position of the phenyl moiety.

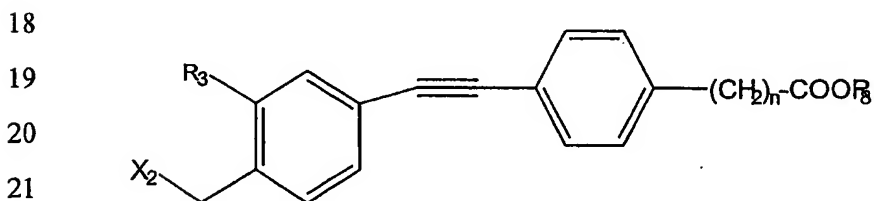
10 **99.** A compound in accordance with Claim 94 where X_2 is 1-
11 imidazolyl, lower alkyl or halogen substituted 1-imidazolyl.

12 **100.** A compound in accordance with Claim 94 where Y is H, lower
13 alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl, or
14 halogen.

15 **101.** A compound in accordance with Claim 94 where A is phenyl.

16 **102.** A compound in accordance with Claim 94 where n is 1.

17 **103.** A compound of the formula



23 wherein R_3 is alkyl of 1 to 6 carbons;

24 X_2 is 1-imidazolyl, OR_7 , or NRR_7 where R is alkyl of 1 to 6 carbons
25 or cyclopropyl, and R_7 is alkyl of 1 to 6 carbons, cyclopropyl or lower alkyl
26 substituted cyclopropyl;

27 n is 0 or 1, and

1 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
2 acceptable base.

3 104. A compound in accordance with Claim 103 wherein X_2 is 1-
4 imidazolyl.

5 105. A compound in accordance with Claim 104 wherein n is 0.

6 106. A compound in accordance with Claim 105 which is selected
7 from the group consisting of 4-(4-imidazol-1-yl-methyl-3-methyl-
8 phenylethynyl)-benzoic acid and [4-(4-imidazol-1-yl-methyl-3-isopropyl-
9 phenylethynyl)-phenyl]-benzoic acid or a salt of said compound with a
10 pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

11 107. A compound in accordance with Claim 104 wherein n is 1.

12 108. A compound in accordance with Claim 107 which is selected
13 from the group consisting of [4-(4-imidazol-1-yl-methyl-3-methyl-
14 phenylethynyl)-phenyl]-acetic acid and [4-(4-imidazol-1-yl-methyl-3-
15 isopropyl-phenylethynyl)-phenyl]-acetic acid or a salt of said compound
16 with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of said
17 compound.

18 109. A compound in accordance with Claim 103 where X_2 is
19 ethyl, cyclopropyl-N-.

20 110. A compound in accordance with Claim 109 wherein n is 0.

21 111. A compound in accordance with Claim 110 which is selected
22 from the group consisting of 4-{4-[(cyclopropyl-ethyl-amino)-methyl]-3-
23 methyl-phenylethynyl}-benzoic and 4-{4-[(cyclopropyl-ethyl-amino)-
24 methyl]-3-isopropyl-phenylethynyl}-benzoic acid or a salt of said
25 compound with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of
26 said compound.

27 112. A compound in accordance with Claim 109 wherein n is 1.

28 113. A compound in accordance with Claim 112 which is (4-{4-

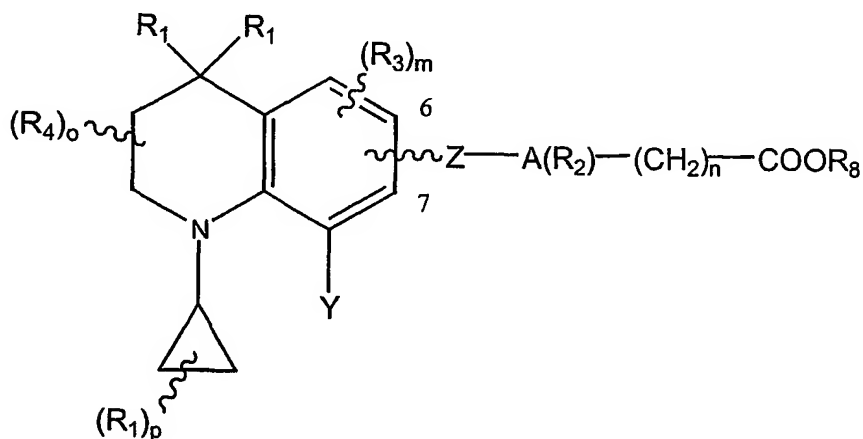
1 [(cyclopropyl-ethyl-amino)-methyl]-3-methyl-phenylethynyl}-phenyl)-acetic
 2 acid or a salt of said compound with a pharmaceutically acceptable base or a
 3 C₁₋₆ alkyl ester of said compound.

4 114. A compound in accordance with Claim 103 where X₂ is (1-
 5 methyl)cyclopropyl-oxy.

6 115. A compound in accordance with Claim 114 wherein n is 1.

7 116. A compound in accordance with Claim 115 which is {4-[3-
 8 isopropyl-4-(1-methyl-cyclopropoxymethyl)-phenylethynyl]-phenyl}-acetic
 9 acid or a salt of said compound with a pharmaceutically acceptable base or a
 10 C₁₋₆ alkyl ester of said compound.

11 117. A compound of the formula



22 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
 23 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
 24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and
 25 heteroaryl groups being optionally substituted with one or two R₂ groups;

26 Y is H, alkyl of 1 to 10 carbons, benzyl, lower alkyl or halogen
 27 substituted benzyl, fluoro-substituted alkyl of 1 to 10 carbons, cycloalkyl of

- 1 3 to 6 carbons, lower alkyl substituted cycloalkyl of 3 to 6 carbons, F, Cl,
2 Br, or I;
- 3 Z is -C≡C-,
4 -(CR₁=CR₁)_n, where n' is an integer having the value 1 - 5,
5 -CO-NR₁-,
6 NR₁-CO-,
7 -CO-O-,
8 -O-CO-,
9 -CS-NR₁-,
10 NR₁-CS-,
11 -CO-S-,
12 -S-CO-,
13 -N=N-;
- 14 R₁ is independently H or alkyl of 1 to 6 carbons;
15 p is an integer having the values of 0 to 5;
- 16 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃,
17 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
18 alkylthio of 1 to 6 carbons;
- 19 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
20 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
21 alkylthio of 1 to 6 carbons or benzyl;
- 22 m is an integer having the values 0 to 2;
- 23 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
24 alkyl of 1 to 6 carbons, or halogen;
- 25 o is an integer having the values of 0 to 4;
26 n is an integer having the values of 0 to 4, and
- 27 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
28 pharmaceutically acceptable base.

1 118. A compound in accordance with Claim 117 where A is phenyl,
2 naphthyl, pyridyl, thienyl or furyl.

3 119. A compound in accordance with Claim 117 where n is 0, 1 or
4 2.

5 120. A compound in accordance with Claim 117 where Z is $-C\equiv C-$, -
6 $CO-NR_1-$,
7 $-CO-O-$, or $-(CR_1=CR_1)_n$, where n' is 1.

8 121. A compound in accordance with Claim 117 where the Z group
9 is attached to the 6-position of the bicyclic moiety.

10 122. A compound in accordance with Claim 117 where Y is H,
11 lower alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl,
12 or halogen.

13 123. A compound in accordance with Claim 117 where A is phenyl.

14 124. A compound in accordance with Claim 117 where n is 1.

15 125. A compound of the formula

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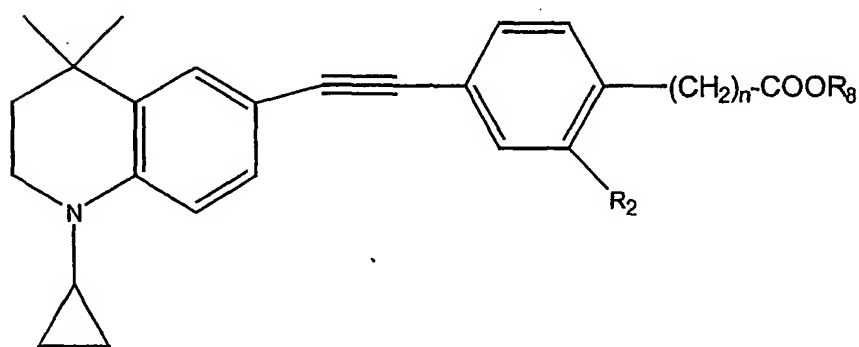
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25 wherein R_2 is hydrogen, alkyl of 1 to 6 carbons, or halogen

26 n is 0 or 1, and

27 R_8 is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
28 acceptable base.

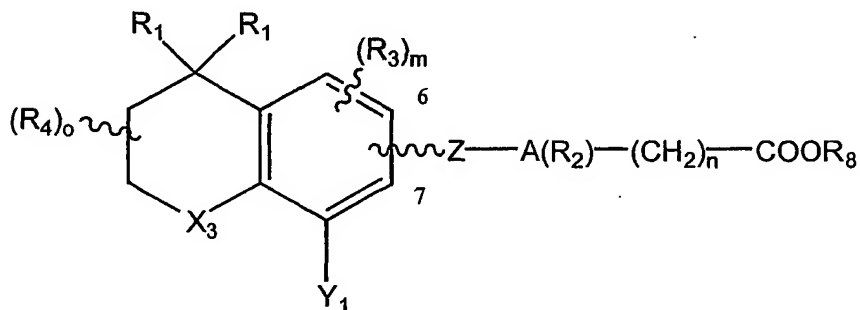
1 126. A compound in accordance with Claim 125 wherein n is 0.

2 127. A compound in accordance with Claim 126 which is 4-(1-
3 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl-ethynyl)-benzoic
4 acid or a salt of said compound with a pharmaceutically acceptable base or a
5 C_{1-6} alkyl ester of said compound.

6 128. A compound in accordance with Claim 125 wherein n is 1.

7 129. A compound in accordance with Claim 128 which is [4-(1-
8 cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl-ethynyl)phenyl]
9 acetic acid methyl ester.

10 130. A compound of the formula



18 wherein A is a phenyl or naphthyl group, or heteroaryl selected from
19 a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
20 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and
21 heteroaryl groups being optionally substituted with one or two R_2 groups;

22 X_3 is S, or O, $C(R_1)_2$, or CO;

23 Y_1 is H, lower alkyl of 1 to 3 carbons, cycloalkyl of 3 to 6 carbons,
24 benzyl, lower alkyl substituted cycloalkyl of 3 to 6 carbons;

25 Z is $-C\equiv C-$,

26 $-(CR_1=CR_1)_n$, where n' is an integer having the value 1 - 5,

27 $-CO-NR_1-$,

1 NR₁-CO-,
2 -CO-O-,
3 -O-CO-,
4 -CS-NR₁-,
5 NR₁-CS-,
6 -CO-S-,
7 -S-CO-,
8 -N=N-;

9 R₁ is independently H or alkyl of 1 to 6 carbons;

10 R₂ is independently H, alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃,
11 fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 6 carbons, or
12 alkylthio of 1 to 6 carbons;

13 R₃ is independently alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
14 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons,
15 alkylthio of 1 to 6 carbons or benzyl;

16 m is an integer having the values 0 to 2;

17 R₄ is independently H, alkyl of 1 to 6 carbons, or F; fluorosubstituted
18 alkyl of 1 to 6 carbons, or halogen;

19 o is an integer having the values of 0 to 4;

20 n is an integer having the values of 0 to 4, and

21 R₈ is H, alkyl of 1 to 6 carbons, -CH₂O(C₁₋₆-alkyl), or a cation of a
22 pharmaceutically acceptable base, the compound meeting at least one of the
23 provisos selected from the group consisting of:

24 Y₁ is cycloalkyl,

25 when Y₁ is not cycloalkyl then X₃ is O or S and n is 1,

26 when Y₁ is not cycloalkyl then X₃ is CO, and n is 1,

27 when Y₁ is not cycloalkyl then X₃ is CO and the moiety A is
28 substituted with at least one F group.

1 131. A compound in accordance with Claim 130 where A is phenyl,
2 naphthyl, pyridyl, thienyl or furyl.

3 132. A compound in accordance with Claim 130 where n is 0, 1 or
4 2.

5 133. A compound in accordance with Claim 130 where Z is $-C\equiv C-$, -
6 $CO-NR_1-$,
7 $-CO-O-$, or $-(CR_1=CR_1)_n$, where n' is 1.

8 134. A compound in accordance with Claim 130 where the Z group
9 is attached to the 6-position of the bicyclic moiety.

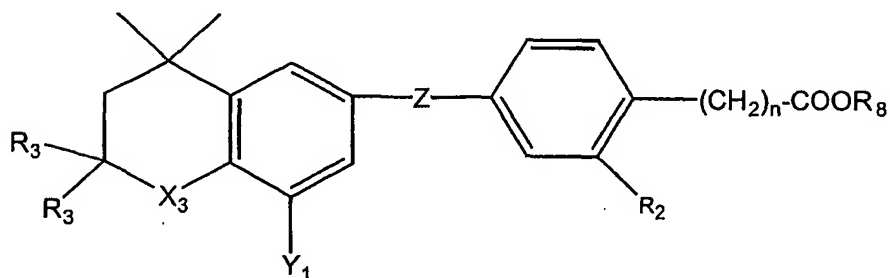
10 135. A compound in accordance with Claim 130 where Y_1 is H,
11 lower alkyl of 1 to 3 carbons, cycloalkyl, lower alkyl substituted cycloalkyl.

12 136. A compound in accordance with Claim 130 where A is phenyl.

13 137. A compound in accordance with Claim 130 where n is 1.

14 138. A compound in accordance with Claim 130 where X_3 is O or
15 CO.

16 139. A compound of the formula



24 wherein R_2 is H or F;

25 R_3 is H or lower alkyl of 1 to 6 carbons;

26 X_3 is O or CO;

27 Y_1 is H, alkyl of 1 to 6 carbons, or cyclopropyl;

- 1 Z is -C≡C- or -CO-O-;
- 2 n is 0 or 1, and
- 3 R₈ is H, alkyl of 1 to 6 carbons, or a cation of a pharmaceutically
- 4 acceptable base, the compound meeting at least one of the provisos selected
- 5 from the group consisting of:
- 6 Y₁ is cyclopropyl,
- 7 when Y₁ is not cyclopropyl then X₃ is O and n is 1,
- 8 when Y₁ is not cyclopropyl then X₃ is CO, and n is 1,
- 9 when Y₁ is not cyclopropyl then X₃ is CO and the moiety A is
- 10 substituted with at least one F group.
- 11 140. A compound in accordance with Claim 139 wherein Z is -C≡C-
- 12 .
- 13 141. A compound in accordance with Claim 140 wherein X₃ is CO,
- 14 Y₁ is H and n is 0.
- 15 142. A compound in accordance with Claim 141 which is 2-fluoro-
- 16 4-(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl-ethynyl)-benzoic
- 17 acid or a salt of said compound with a pharmaceutically acceptable base or a
- 18 C₁₋₆ alkyl ester of said compound.
- 19 143. A compound in accordance with Claim 140 wherein X₃ is CO,
- 20 Y₁ is H and n is 1.
- 21 144. A compound in accordance with Claim 143 which is selected
- 22 from the group consisting of 4-[(8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-
- 23 naphthalene-2-yl-ethynyl)-phenyl]-acetic acid and [2-fluoro-4-(8,8-
- 24 dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-yl-ethynyl)phenyl]-acetic
- 25 acid or a salt of said compound with a pharmaceutically acceptable base or a
- 26 C₁₋₆ alkyl ester of said compound.
- 27 145. A compound in accordance with Claim 140 wherein X₃ is O,

1 Y_1 is H and n is 0.

2 146. A compound in accordance with Claim 145 which is 2-fluoro-
3 4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a salt of said
4 compound with a pharmaceutically acceptable base or a C_{1-6} alkyl ester of
5 said compound.

6 147. A compound in accordance with Claim 140 wherein X_3 is O,
7 Y_1 is H or ethyl and n is 1.

8 148. A compound in accordance with Claim 147 which is selected
9 from the group consisting of [4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)
10 phenyl] acetic acid, [2-fluoro-4-(2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)
11 phenyl] acetic acid and [4-(8-ethyl-2,2,4,4-tetramethyl-chroman-6-yl-
12 ethynyl) phenyl] acetic acid or a salt of said compound with a
13 pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

14 149. A compound in accordance with Claim 140 wherein X_3 is O,
15 Y_1 is cyclopropyl and n is 0.

16 150. A compound in accordance with Claim 149 which is 4-(8-
17 cyclopropyl-2,2,4,4-tetramethyl-chroman-6-yl-ethynyl)-benzoic acid or a
18 salt of said compound with a pharmaceutically acceptable base or a C_{1-6}
19 alkyl ester of said compound.

20 151. A compound in accordance with Claim 140 wherein X_3 is O,
21 Y_1 is cyclopropyl and n is 1.

22 152. A compound in accordance with Claim 151 which is selected
23 from the group consisting of [4-(8-cyclopropyl-2,2,4,4-tetramethyl-
24 chroman-6-yl-ethynyl) phenyl] acetic acid and [4-(8-cyclopropyl-2,2,4,4-
25 tetramethyl-chroman-6-yl-ethynyl)-2-fluorophenyl] acetic acid or a salt of
26 said compound with a pharmaceutically acceptable base or a C_{1-6} alkyl ester
27 of said compound.

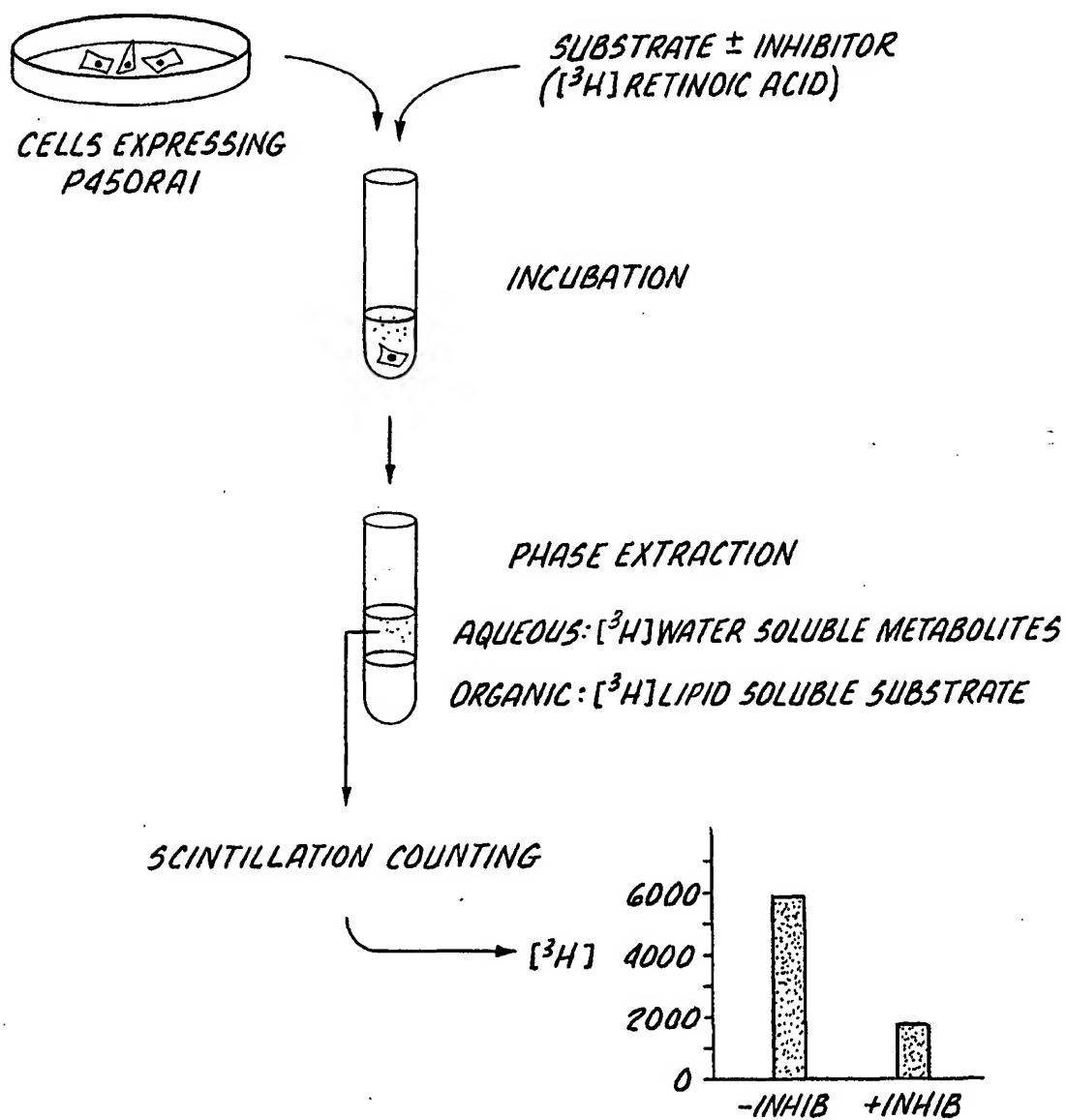
28 153. A compound in accordance with Claim 139 where Z is -CO-O-,

1 X_3 is CO and n is 1.

2 **154.** A compound in accordance with Claim 153 which is 8,8-
3 dimethyl-5-oxo-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid-4-
4 (carboxymethyl)phenyl ester or a salt of said compound with a
5 pharmaceutically acceptable base or a C_{1-6} alkyl ester of said compound.

6 **155.** A compound in accordance with Claim 139 where Z is -CO-O-,
7 X_3 is O and n is 1.

8 **156.** A compound in accordance with Claim 155 which is 2,2,4,4-
9 tetramethyl-chroman-6-carboxylic acid 4-(carboxymethyl)phenyl ester or a
10 salt of said compound with a pharmaceutically acceptable base or a C_{1-6}
11 alkyl ester of said compound.



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/018361 A3

(51) International Patent Classification⁷: C07D 311/74,
335/06, 215/06, C07C 229/46, 65/19, C07D 217/04, C07C
57/38, C07D 521/00, C07C 59/82, A61K 31/47, 31/352,
31/192, A61P 29/00, 31/12

09/651,566 29 August 2000 (29.08.2000) US

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(21) International Application Number: PCT/US01/25443

(22) International Filing Date: 14 August 2001 (14.08.2001)

(25) Filing Language: English

(26) Publication Language: English

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(30) Priority Data:

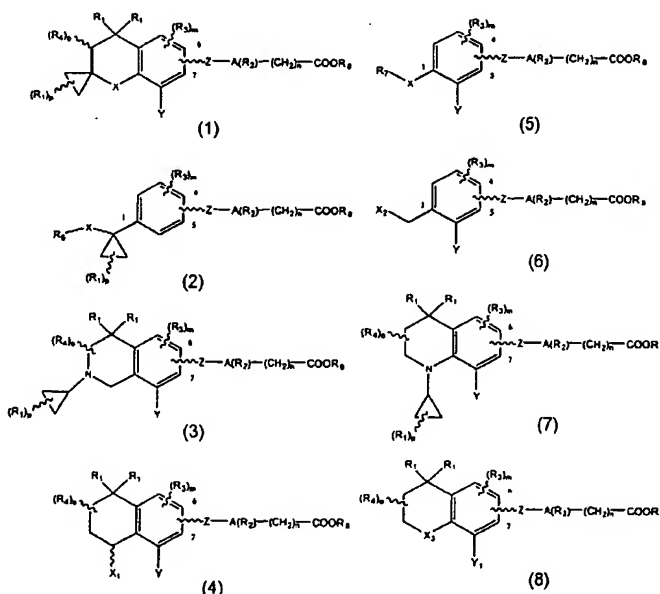
09/651,235	29 August 2000 (29.08.2000)	US
09/651,004	29 August 2000 (29.08.2000)	US
09/651,003	29 August 2000 (29.08.2000)	US
09/651,564	29 August 2000 (29.08.2000)	US
09/651,234	29 August 2000 (29.08.2000)	US
09/651,234	29 August 2000 (29.08.2000)	US
09/651,001	29 August 2000 (29.08.2000)	US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

[Continued on next page]

(54) Title: COMPOUNDS HAVING ACTIVITY AS INHIBITORS OF CYTOCHROME P450RAI



(57) Abstract: Compounds having the Formulas 1 through 8, wherein the symbols have the meaning defined in the specification are inhibitors of the cytochrome P450RAI (retinoic acid inducible) enzyme, and are used for treating diseases responsive to treatment by retinoids.



LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

Published:

— with international search report

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
31 July 2003

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INTERNATIONAL SEARCH REPORT

International Application No

PCT. 01/25443

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D311/74 C07D335/06 C07D215/06 C07C229/46 C07C65/19
 C07D217/04 C07C57/38 C07D521/00 C07C59/82 A61K31/47
 A61K31/352 A61K31/192 A61P29/00 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 089 509 A (CHANDRARATNA) 18 February 1992 (1992-02-18) column 4, line 1 - line 31; claims; examples ---	117-129
Y	US 5 739 338 A (BEARD ET. AL.) 14 April 1998 (1998-04-14) column 4, line 44 - column 5, line 20; claims; examples ---	117-129
Y	US 5 023 341 A (CHANDRARATNA) 11 June 1991 (1991-06-11) column 1, line 41 - line 53; claims; examples --- -/--	1-25, 50-61

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 June 2002

Date of mailing of the international search report

10.05.03

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INTERNATIONAL SEARCH REPORT

International Application No

PCT. 01/25443

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 134 159 A (CHANDRARATNA) 28 July 1992 (1992-07-28) column 5, line 32 - line 55; claims; examples ---	1-25, 50-61
Y	US 5 965 606 A (TENG ET. AL.) 12 October 1999 (1999-10-12) column 1, line 15 - line 67; claims; examples ---	1-25, 50-61, 117-129
Y	US 5 015 658 A (CHANDRARATNA) 14 May 1991 (1991-05-14) claims; examples ---	1-25, 50-61, 117-129
Y	US 5 045 551 A (CHANDRARATNA) 3 September 1991 (1991-09-03) claims; examples ---	1-25, 50-61, 117-129
X	EP 0 130 795 A (PFIZER INC.) 9 January 1985 (1985-01-09) claims; example 2 ---	130-138
X	US 5 202 471 A (CHANDRARATNA) 13 April 1993 (1993-04-13) column 23, compounds 2, 9, 11 and 59 ---	80-84, 86,87
X	US 5 498 795 A (SONG ET. AL.) 12 March 1996 (1996-03-12) column 24, compounds 18 and 19 ---	80-87
X	US 5 489 584 A (VULIGONDA ET. AL.) 6 February 1996 (1996-02-06) column 21, compound 56 and column 22, compound 57 ---	62-68
X	WO 96 20930 A (ALLERGAN) 11 July 1996 (1996-07-11) tables 1,5 -----	62-66,68

INTERNATIONAL SEARCH REPORT

Int'l application No.
CT/US 01/25443

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
all additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-25, 50-61, 117-129

Bicyclic compounds having a cyclopropyl substituent.

2. Claims: 26-49, 80-116

Monocyclic compounds having a cyclopropyl substituent.

3. Claims: 62-79, 130-156

Other substituted bicyclic compounds.

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